Serial No: 10/600,674
AP

(19) Europäisch s Patentamt
European Patent Office
Offic uropéen des brev ts

(11) Publication number: **0 470 039 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **07.12.94**

(51) Int. Cl.5: **C07D 209/08**, C07D 231/56, C07D 401/12, C07D 401/14, C07D 209/10, C07D 401/04, C07D 405/04, C07D 405/14, C07D 409/04, C07D 409/14, A61K 31/40, A61K 31/415

(21) Application number: **91610058.9**

(22) Date of filing: **22.07.91**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Novel 3-arylindole and 3-arylindazole derivatives.**

(30) Priority: **30.07.90 DK 1811/90**

(43) Date of publication of application:
05.02.92 Bulletin 92/06

(45) Publication of the grant of the patent:
07.12.94 Bulletin 94/49

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 135 781
EP-A- 0 200 322
DE-A- 2 811 031

CHEMICAL & PHARMACEUTICAL BULLETIN vol. 33, no. 5, May 1985, JAPAN pages 1826 - 1835; MAKOTO ADACHI ET AL.: 'Aminohaloborane in Organic Synthesis IX.Exclusive ortho Acylation Reaction of N-Monoaminoalkylanilines'

J.-M. Meunier, A. Shvaloff, Neurotransmitteurs, MASSON, p.227

(73) Proprietor: **H. LUNDBECK A/S**
Ottiliavej 7-9
DK-2500 Kobenhavn-Valby (DK)

(72) Inventor: **Perregaard, Jens Kristian**
22, Thyrasvej
DK-3630 Jaegerspris (DK)
Inventor: **Andersen, Kim**
100 CI, Vesterbrogade
DK-1620 Copenhagen-V (DK)

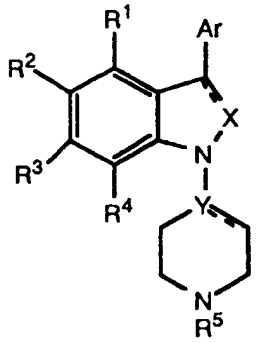
(74) Representative: **Petersen, John Meidahl**
c/o H. Lundbeck A/S
Patent Department
Ottiliavej 7-9
DK-2500 Copenhagen-Valby (DK)

EP 0 470 039 B1

Description

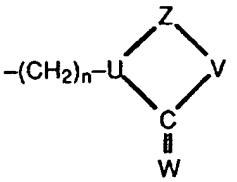
The present invention relates to novel 3-arylindole or 3-arylindazole derivatives and their acid addition salts with selective and long lasting central serotonin S_2 (5-hydroxytryptamine-2 ; 5-HT_2) antagonistic activity, to methods for preparing such compounds, to medicaments comprising such compounds as an active ingredient and to the benificial use of these derivatives in the treatment of CNS disorders such as anxiety, agression, depression, sleep disturbances, migraine, negative symptoms of schizophrenia, and Parkinson's disease with a low degree of undesired side effects.

The novel indole and indazole derivatives of the present invention are represented by the following formula :



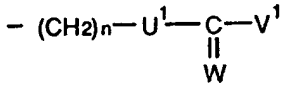
I

wherein Ar is phenyl optionally substituted with one or more substituents selected from halogen, hydroxy, trifluoromethyl, and cyano, or Ar is 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;
R^1-R^4 are independently selected from hydrogen, halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulphonyl, cyano, trifluoromethyl, or trifluoromethylthio;
the dotted line emanating from X in the ring system designates an optional bond; when said dotted line indicates a bond, X is nitrogen or a group CR^6 wherein R^6 is hydrogen, halogen, trifluoromethyl or lower alkyl;
when the dotted line indicates no bond, X is CH_2 ;
the dotted line, emanating from the Y, indicates an optional bond;
when it does not indicate a bond Y is N or CH; and when it indicates a bond Y is C;
R^5 is hydrogen, or lower alkyl, optionally substituted with one or two hydroxy groups, or R^5 is a group taken from structures **1a** and **1b**:



1a.

or



1b.

wherein n is an integer from 2 - 6;
W is oxygen or sulphur;
U is nitrogen or CH ;
Z is $-(CH_2)_m-$, m being 2 or 3, or Z is 1,2-phenylene optionally substituted with halogen or trifluoromethyl or Z is -CH=CH-, $-COCH_2-$ or $-CSCH_2-$;
V is oxygen, CH_2, or NR^7, wherein R^7 is hydrogen or lower alkyl or alkenyl, cycloalkyl or cycloalkylalkyl optionally substituted with one or two hydroxy groups;
U^1 is a group NR^8, wherein R^8 is hydrogen or lower alkyl or alkenyl, cycloalkyl or cycloalkylalkyl optionally substituted with one or two hydroxy groups; and
V^1 is NR^9R^{10}, where each of R^9 and R^{10} may be independently selected among the R^8-substituents;
provided that R^5 may not be methyl when R^1-R^4 each are hydrogen, X and Y are CH and Ar is phenyl.

Stereoisomers, prodrugs and pharmaceutically acceptable salts of the compounds of formula I are also embraced by the invention.

The term "lower alkyl" is intended to mean a straight or branched alkyl group having from one to four carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, etc. Lower alkoxy, lower alkylthio and lower alkylsulfonyl similarly designate such groups wherein the alkyl moiety is a lower alkyl group as defined above.

Lower alkenyl is intended to mean an alkenyl group containing from 2 to 4 carbon atoms, for example ethenyl, 1-propenyl, 2-butenyl, etc.

Cycloalkyl means cycloalkyl having from three to eight carbon atoms inclusive.

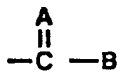
Halogen means fluoro, chloro, bromo or iodo.

The term "indicate an optional bond" is intended to mean that the dotted lines may or may not represent a bond, i.e. that the rings may or may not have a double bond in the positions of the dotted lines in Formula I.

The Z groups $-COCH_2-$ and-$CSCH_2-$ may be incorporated in the ring of the structure 1a in both directions.

The acid addition salts of the invention are pharmaceutically acceptable salts of the compounds of Formula I formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulphonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

Prodrugs of the present invention may be conventional esters with available hydroxy groups, or in particular if the compound is a compound of the general formula I wherein R^5 is a group of the structure **1a** wherein V is NH or the structure **1b** where U^1 is NH and/or V^1 is NHR^{10} they may exist as prodrugs in which said nitrogen atom is acylated with a group



wherein A is O, S or NR^a with R^a being hydrogen, lower alkyl, or phenyl optionally substituted with one or more substituents selected from the group comprising halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio and cyano;

B is a group R^b which is alkyl or alkenyl containing from one to twentyfour carbon atoms inclusive, or cycloalkyl or cycloalkylalkyl, optionally substituted with one or two hydroxy groups, phenyl optionally substituted with one or more substituents selected from the group comprising halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, or cyano; or

B is $QR^{b'}$, wherein Q is O or S and $R^{b'}$ is one of the substituents defined for R^b above; or

B is NR^cR^d, wherein R^c and R^d independently are either hydrogen or one of the substituents defined for R^b above.

Although the latter prodrugs are not esters , they have been found to decompose properly in order to release the compound of the invention over a desired prolonged period of time when administered parenterally as a depote formulation in an apropriate oil, such as peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, coconut oil (e.g. viscoleo®), etc., or synthetic esters of fatty acids and glycerol or propylenglycol.

Only one 3-arylindole or 3-arylindazole derivative substituted in the 1-position with a piperidinyl, piperazinyl or tetrahydropyridyl group is known from the prior art.

1-(1-methyl-4-piperidinyl)-3-phenylindole is disclosed in Adachi et al, *Chem. Pharm. Bull., 33(5)*, 1826-1835, (1985), as an intermediate in the synthesis of 2-acyl-N-(1-methyl-4-piperidinyl)aniline. Nothing is disclosed or suggested as regards the pharmacological properties of said compound.

On the other hand indole or indazole derivatives having an aryl substituent in the 1-position and a tetrahydropyridyl, piperidinyl or piperzinyl group in the the 3 position have been disclosed in a number of patents.

DE Offentlegungsschrift No. 2811031 (Laboratories Sauba S.A.) relates to 1-(optionally subst. phenyl)-3-((4-alkyl or aryl)-piperazin-1-yl)-indole derivatives stated to have antinflammatory activity.

EP-A2 224919 (Fujisawa Pharmaceutical Co., Ltd.) discloses 1-phenyl-3-(4-(thiazolylalkyl)piperazin-1-yl)-indole derivatives as antiallergy agents.

DE Offenlegungsschrift No. 1695604 (Pfizer Corporation) describes 1-phenyl-3-(optionally 1-benzyl or 1-methyl substituted 4-piperidinyl)-2-indolones having anti-depressant effects.

EP-A 0 135 781 and US Patents Nos. 4,670,447 , 4,758,668 and 4,853,470 all generically relate to a very broad class of 1-aryl-3-pipendylindazoles alleged to have analgesic and antipsychotic and in some of the patents also antidepressant effects. Antipsychotic effects are shown by the apomorphine climbing assay which is a test for classical neuroleptic activity, i.e. dopamine antagonism, and antidepressant effects are shown in the tetrabenazine ptosis test for a few compounds.

EP-A 0 281 309 and US Patents No. 4,831,031 disclose 3-[4-(heterocycleethyl (or -butyl))piperazin-1-yl]indazoles substituted in the 1-position with trifluoromethylphenyl and claimed to be useful as antipsychotics as shown in the apomorphine climbing test.

European Patent Publication No. 0 302 423 relates to 1-phenyl-3-(1-piperazinyl)-1*H*-indazoles claimed to be useful as analgesics, anticonvulsants and antidepressants, the antidepressant effects again shown in the tetrabenazine ptosis test in mice. Only results for a few compounds showing quite weak effects are given.

From our own US patent No 4,710,500 (corresponding to EP patent No 0200323) 1-aryl-3-(1,2,3,6-tetrahydropyridin-4-yl)-, 1-aryl-3-(4-piperidinyl)- and 1-aryl-3-(1-piperazinyl)-indole derivatives are known. The compounds are claimed to be potent and long-lasting dopamine antagonists, and accordingly to be useful in the treatment of psychoses and additionally to be strong 5-HT_2 antagonists indicating effects in the treatment of depression, negative symptoms of schizophrenia and neuroleptic-induced extrapyramidal side effects and cardiovascular diseases. Some of the compounds are selective 5-HT_2 antagonists *in vivo*.

Previously evidence of various clinical effects of 5-HT_2 antagonists have been presented. For example reference may be made to the following:

The selective 5-HT_2 antagonist ritanserin has been shown to be an antidepressant and to improve depressive symptoms of schizophrenia (E. Klieser, W. H. Strauss; Pharmacopsychiat. 21 (1988), pp. 391-393) and it has been demonstrated to exert effects in an animal test reminiscent of anxiolytic drug activity (F.C. Colpart et al; Psychopharmacology (1985) 86; 303-305). Furthermore ritanserin has been shown to improve the quality of sleep (P. A. J. Janssen; Pharmacopsychiat. 21 (1988), 33-37).

Furthermore it is generally believed that 5-HT is involved in migraine attacks. The links between 5-HT and migraine attacks are several and they suggest a number of mechanisms whereby 5-HT may be involved (Scrip Report; "Migraine - Current trends in research and treatment"; PJB Publications Ltd.; May 1991). Various 5-HT_2 antagonists are in clinical trials as anti-migraine agents, such as sergolexole (c.f. for example Pharma Projects , May 1991, 1359-1365).

Studies of the mixed serotonin and dopamine receptor antagonist setoperone indicate that blockade of 5-HT_2 receptors may be related to improvement of negative symptoms of schizophrenia (Ceulemans et al, Psychopharmacology (1985) 85, 329-332).

Finally, ritanserin has been found to relieve neuroleptic-induced parkinsonism (Bersani et al.; Clinical Neuropharmacology, 13, No. 6 (1990), 500-506).

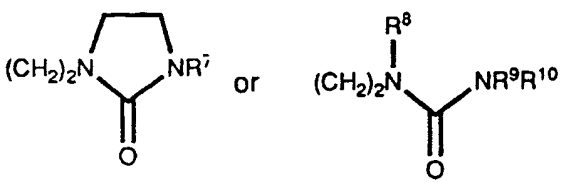
Surprisingly, it has now been found that the novel indole or indazole derivatives of the present invention are selective 5-HT_2 antagonists with prolonged activity, and accordingly are useful in the treatment of anxiety, agression, depression, sleep disturbances, migraine, negative symptoms of schizophrenia, drug-induced Parkinsonism and Parkinson's disease substantially without causing neurological side effects.

The compounds of the present invention are selective, and most of them very selective, antagonists of the 5-HT_2 receptor, measured as the ratio between the dopamine D-2 receptor and the 5-HT_2 receptor antagonistic activities. Only a few compounds with such a selectivity profile are known from the prior art. Such compounds include ritanserin, seganserin, ICI 169369, ICI 170809, sergolexole and MDL 11939, which compounds are very different in chemical structure from the present compounds.

A preferred subgroup of compounds are those wherein X is a CR^6 group; most preferably those wherein R^2 and/or R^6 are other than hydrogen.

Preferably, Ar is phenyl optionally substituted with halogen, most preferably 4-fluorophenyl;

R^5 is a group



wherein R^7, R^8,
R^9 and R^{10} independently are selected from hydrogen, lower alkyl or alkenyl; R^2 is selected from halogen, $-CF_3$, and $-CH_3$; R^3 is selected from H, halogen, $-CF_3$, and $-CH_3$; and R^1 and R^4 are H.

Particularly preferred compounds are:
5-Chloro-3-(4-fluorophenyl)-1-[1-[2-(3-methylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole,
3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indole,
3-(4-Fluorophenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl)-*1H*-indole,
2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-*1H*-indole,
2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole,
2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-4-piperidyl)-*1H*-indole, and 1-[1-[2-(1,3-Dimethyl-1-ureido)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole.

In another aspect the present invention provides a pharmaceutical preparation comprising at least one compound of the Formula I as an active ingredient together with a pharmaceutically acceptable carrier or diluent.

The compounds of the Formula I and the pharmaceutically acceptable acid addition salts thereof may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection.

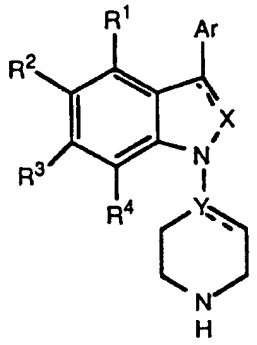
Suitable pharmaceutical preparations may be prepared by methods well known in the art. Conveniently, the compounds of the invention are administered in unit dosage form containing said compound in an amount of about 0.10 - 100 mg, preferably about 1 - 50 mg.

The total daily dose usally ranges from about 0.1 to 500 mg of the active compound of the invention. In a further aspect the present invention provides the use of a compound of the Formula I for the manufacturing of a pharmaceutical preparation for the treatment of CNS disorders.

The present invention also provides a method for treating CNS disorders comprising administration of a compound having the general Formula I or an acid addition salt thereof to a patient suffering from such a disease.

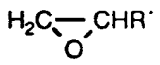
Finally, the present invention provides a method for the preparation of a derivative having the general Formula I, which method comprises:

a) reacting a compound of the following formula:

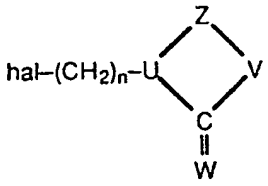


II

wherein R^1, R^2, R^3, R^4, X, Y, Ar and the dotted lines are as defined above, with a lower alkyl halide, alkyl mesylate or tosylate, with an epoxide of the formula

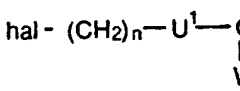


wherein R' is hydrogen, methyl or ethyl or with a halide of the general formula



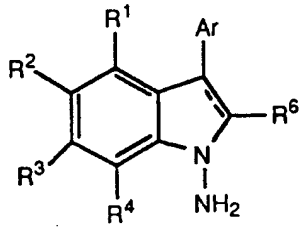
III a

or



III b

wherein n, W, U, V, Z, V^1 and U^1 are as defined above;
b) reacting a compound of following formula:

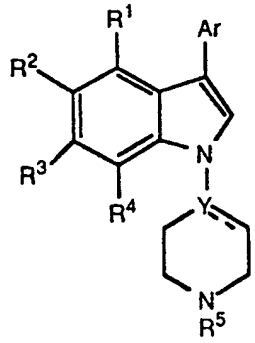


IV

wherein R^1, R^2, R^3, R^4, R^6, Ar and the dotted line are as defined above, with a compound of the general formula

$R^5N(CH_2CH_2hal)_2$ V

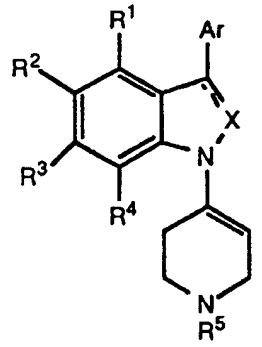
in which R^5 is as defined above and hal is halogen;
c) reducing the indole ring of a compound of the general formula



VI

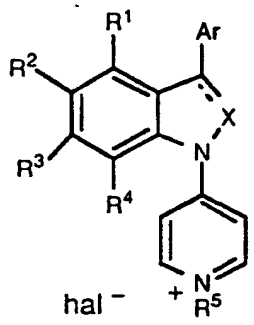
wherein R^1-R^5, Ar, Y and the dotted line are as defined above, to a dihydroindole ring;

d) reducing the double bond in the tetrahydropyridyl ring in a compound of the formula:



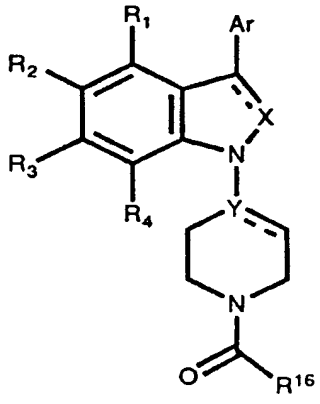
VII

wherein R^1 - R^5, X, Ar and the dotted line are as defined above;
e) reducing the pyridinium ring in a compound of following formula:



VIII

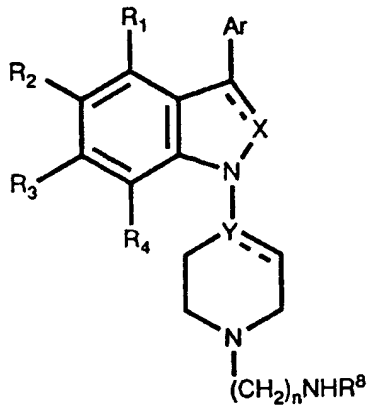
wherein R^1 - R^5, X, Ar and the dotted line are as defined above except that R^5 may not be hydrogen, and hal is halogen, to a tetrahydropyridine ring;
f) reducing the pyridinium ring in a compound of the above Formula **VIII** or the pyridyl ring of a compound of formula **XIV** (below) to a piperidine ring;
g) reducing the carbonyl group of a compound of the following formula:



IX

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined and R^{16} is hydrogen, lower alkyl or lower alkoxy;

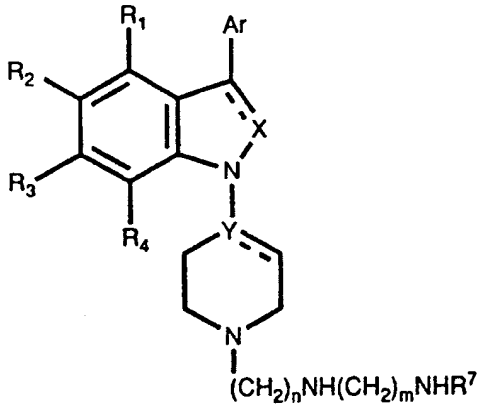
h) acylating an aminoalkyl derivative of the following formula :



X

wherein R^1 - R^4, X, Y, Ar, R^8, n and the dotted lines are as defined above, with an acylating agent such as a carboxylic acid halogenide, anhydride or mixed anhydride, or a carbamyl or thiocarbamyl chloride, an isocyanate, isothiocyanate, or a substituted chloroformate;

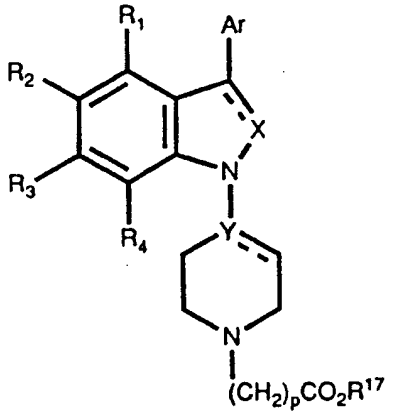
i) ringclosure reaction of an intermediate ethylene or propylene diamine derivative of the following formula :



XI

wherein R^1 - R^4, R^8, n, X, Y, Ar and the dotted lines are as defined above and m is 2 or 3, with phosgene, thiophosgene or carbondisulphide to form a substituent of the structure **1a** ; or

j) reducing a carboxylic acid or carboxylic acid derivative of the following formula :



XII

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined, R^{17} is hydrogen or lower alkyl and p is 1, 2 or 3;

and then, if desired:

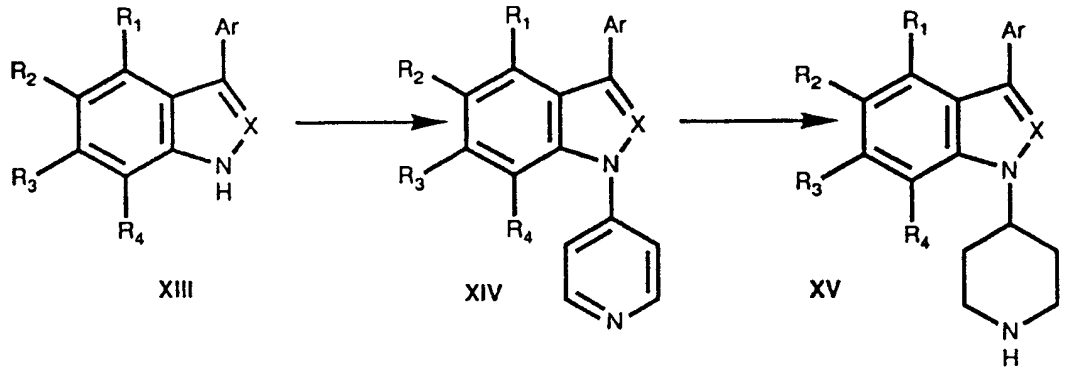
acylating a compound prepared in one of the methods (a) to (j) having the formula **I** in which R^5 is a structure **1a** or **1b** wherein V is NH, or V^1 is NHR^{10} or U^1 is NH with an acylating agent, or esterifying an available hydroxy group in a compound of formula **I** in order to obtain a prodrug;

converting a compound prepared in one of methods (a) to (j) in a pharmaceutically acceptable acid addition salt thereof; or

resolving an optically active compound of formula **I** prepared in one of methods (a) to (j) in optically active isomers thereof.

In method (a) the reaction is conveniently performed at 20-120 °C in an aprotic solvent such as acetone or methyl isobutyl ketone in the presence of free base (e.g. K_2CO_3 or triethylamine) and the starting compounds of Formula **II** are prepared as described below.

3-aryl-1-(4-piperidyl)indoles and 3-aryl-1-(4-piperidyl)indazoles are prepared as shown in the following reaction scheme:



XIII **XIV** **XV**

wherein R^1-R^4, R^5 and Ar are as defined above.

An 3-arylindole or 3-arylindazole of the Formula **XIII** is arylated with 4-chloro- or 4-bromopyridine in NMP, DMF, HMPA or DMSO with potassium carbonate as base and catalyzed by copper, copper(I) iodide or copper(I) bromide at 150-210 °C. The 3-aryl-1-(4-pyridyl)indole or 3-aryl-1-(4-pyridyl)indazole of Formula **XIV** thus obtained is reduced to the 3-aryl-1-(4-piperidyl)indole or 3-aryl-1-(4-piperidyl)indazole of the Formula **XV** with hydrogen at low pressure (3 ato.) in the presence of platinum.

3-Arylindoles, which are unsubstituted in the 2-position, are prepared from the corresponding 2-cyano-3-arylindoles or 3-arylindole-2-carboxylic esters by alkaline or acidic hydrolysis followed by decarboxylation in NMP or quinoline with copper catalysis. The 2-cyano-3-arylindoles and 3-arylindole-2-carboxylic esters

used are prepared either from the corresponding anilines by Japp-Klingemann reaction followed by Fischer indole synthesis or from the corresponding 2-benzoylanilines according to modified literature procedures (Morooka et al, *Synthesis*, **1978**, 445, Hughes et al, *J. Proc. Roy. Soc. N. S. Wales*, **1939**, *72*, 209 and C. D. Jones, *J. Org. Chem.*, **1972**, *37*, 3624).

2-Substituted 3-arylindoles are prepared either from the corresponding 2-benzoyl-anilines or by Fischer indole synthesis from the corresponding substituted phenyl hydrazones (e.g. (4-fluorophenyl)acetone (4-methylphenyl)hydrazone) according to modified literature procedures (Greuter et al, *Helv. Chem. Acta*, **1974**, *57*, 281 and Yamamoto et al, *Chem. Pharm. Bull.*, **1968**, *16*, 2313).

3-Arylindazoles are prepared either from the corresponding 2-benzoylanilines or by heating the corresponding 2-chloro - or bromobenzophenone hydrazone with base, according to modified literature procedures (Dziewonski et al., *Bull. Intern. Acad. Polonaise, Casse Sci. Math. Nat.*, **1935A**, 333 (*Chem. Abstr.*, **1936**, *30*, 1972) and Gladstone et al, *J Chem. Soc.*, **1965**, 3048).

2-Halo-3-aryl-1-(4-piperidyl)indoles are prepared from the corresponding 3-aryl-1-(4-piperidyl)indoles, in which the piperidine nitrogen is protected by a suitable aminoprotective group (e.g. methyl or 2,2,2-trichloroethyl carbamate), by halogenation with an halogenation reagent such as *N*-bromosuccinimide, *N*-chlorosuccinimide or bromine in an inert solvent (e.g. CCl_4 or acetic acid) according to modified literature procedures (Hino et al.,*Tetrahedron*, **1974**, *30*, 2123), followed by deprotection of the piperidine nitrogen by standard methods which are obvious to the chemist skilled in the art.

In method (b) the reaction is performed by refluxing a compound of Formula **IV** with a compound of Formula **V** and a strong base (e.g. sodium amide) in an inert solvent, e.g. toluene. The starting compounds of Formula **IV** are prepared by reacting the corresponding 3-arylindoles, prepared as described above, with hydroxylamine-O-sulphonic acid and strong base (e.g. potasium tert.-butoxide) in a polar aprotic solvent (e.g. DMF).

In method (c) the reduction is conveniently performed with a complex hydride (e.g. sodium borohydride) in acidic solution (e.g.trifluoroacetic acid).

In method (d) the reduction is suitably carried out at a low hydrogen pressure (3 ato.) in the presence of platinum or palladium or by refluxing a compound of formula **VII** with ammonium formate and palladium in a water miscible solvent (e.g. ethanol).

In method (e) the reduction is expediently carried out with a complex hydride (e.g. sodium borohydride in methanol) whereas the reduction in method (f) preferably is performed by catalytic hydrogenation with platinum as a catalyst. The starting compounds of Formula **VIII** are prepared by quaternizing a 1-(4-pyridyl)-3-arylindole or 1-(4-pyridyl)-3-arylindazole, prepared as described above, with a lower alkyl halide or a halide of the general Formula **IIIa** or **IIIb** in MIBK or acetone. The reduction in method (g) is conveniently carried out with lithium aluminum hydride in tetrahydrofuran, or diethyl ether, or with diborane in tetrahydrofuran. Aminoalkyl derivatives of the Formula **X** (method h) are prepared by alkylating a compound of the Formula **II** with a halo-nitrile of the following formula: $hal(CH_2)_nCN$ in the presence of a base (e.g. K_2CO_3 or triethylamine) in an inert solvent such as acetone, MIBK or toluene at elevated temperature (30-100 °C). The cyano group may be reduced according to standard procedures using e.g. AlH_3, $LiAlH_4$ or B_2H_6. The R^9 substituent is introduced by direct alkylation or by an acylation/reduction procedure, which is obvious to the chemist skilled in the art. Acylation of the thus obtained amino derivatives is accomplished by addition of an acylating agent at a low temperature (-20-30 °C) preferably in a chlorinated solvent (dichloromethane, chloroform, or 1,1,1-trichloroethane) and, if necessary, in the presence of a base to neutralize any acidic reaction product formed.

Ethylene or propylene diamines as intermediates for the ringclosure procedure in method (i) are prepared by repeating with appropriate reagents the procedure described for the preparation of the aminoalkyl derivatives used as starting materials in method (h). Generally, heating (80-150 °C) is required to effect ringclosure with the appropriate carbonyl- or thiocarbonyl precursor compound (phosgene, thiophosgene, carbondisulphide, urea or thiourea).

In method (j) the reduction is conveniently carried out using a complex hydride (e.g. lithium aluminum hydride) in an inert solvent (e.g. diethyl ether). The starting compounds of Formula **XII** are prepared by reacting a compound of Formula **II** with a halocarboxylic acid ester of formula $hal\text{-}(CH_2)_pCO_2R^{17}$ in the presence of a base (e.g. K_2CO_3 or triethylamine) in an inert solvent such as acetone, MIBK or toluene at elevated temperature (30-100 °C).

The ω-haloalkyl-2-imidazolidinone alkylating reagents (substructure of structure **IIIa**) were prepared according to modified literature procedures (see eg. Johnston, T.P.; McCaleb, G.S.; Montgomery, J.A. The Synthesis of Antineoplastic Agents. XXXII. N-Nitrosureas. *J.Med.Chem.* **1963**, *6*, 669-681; Ebetino, F.F. *Belg.Patent* 653421, 1965; *Chem.Abstr.* **1966**, *64*, 12684; Costeli, J.; Züst, A. *Ger.Offen* 2035370, 1971; *Chem.Abstr.* **1971**, *74*, 87985z). Other sidechains of structure **IIIa** were prepared as stated in the literature.

The acid addition salts of the compounds of the invention are easily prepared by methods well known in the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or with an excess of the acid in an aqueous immiscible solvent, such as diethyl ether or chloroform, with the desired salt separating directly. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts.

In the following the invention is further illustrated by way of examples, which in no way may be construed as limiting for the invention.

EXAMPLE 1

3-(4-Fluorophenyl)-*1H*-indole **1a**.

Methyl 3-(4-fluorophenyl)-*1H*-indole-2-carboxylate **22d** (59.6 g) was refluxed in a mixture of methanol (1.5 l) and 2 N aqueous NaOH (500 ml) for 3.5 h. The reaction mixture was cooled to room temperature, the solvents were evaporated *in vacuo* and water (500 ml) was added. The alkaline solution was acidified and the thus formed precipitate was filtered off and dissolved in ethyl acetate (750 ml). The ethyl acetate solution was washed with brine (500 ml) and dried (Na_2SO_4). Evaporation of the solvents afforded the crude 4-fluorophenyl-*1H*-indole-2-carboxylic acid which was used without further purification.
A mixture of the crude indole-2-carboxylic acid (55.0 g), Cu (2.0 g) and quinoline (1.0 l) was refluxed for 2.5 h, cooled and filtered. The filtrate was poured into water (800 ml) and extracted with diethyl ether (2 x 800 ml). The combined organic phases were succesively washed with 1 N hydrochloric acid (4 x 1.0 l), washed with brine (1.0 l) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave the title compound which was precipitated from diethyl ether. Yield: 43.6 g, mp 98-100 °C.
In a corresponding manner the following indole derivatives were prepared:
5-Chloro-3-(4-fluorophenyl)-*1H*-indole **1b**, mp 81-83 °C.
3-(4-Fluorophenyl)-5-methyl-*1H*-indole **1c**, mp 123-126 °C.
6-Chloro-3-(4-fluorophenyl)-*1H*-indole **1d**, (oil).
5-Fluoro-3-(4-fluorophenyl)-*1H*-indole **1e**, (oil).
3-(4-Fluorophenyl)-5-trifluoromethyl-*1H*-indole **1f**, (oil).
5-Chloro-3-phenyl-*1H*-indole **1g**, mp 84-86 °C.

EXAMPLE 2

3-(4-Fluorophenyl)-1-(4-pyridyl)-*1H*-indole **2a**.

3-(4-Fluorophenyl)-*1H*-indole **1a** (39.3 g), 4-chloropyridine hydrochloride (55.8 g), K_2CO_3 (102.8 g), CuBr (15 g) and N-methylpyrrolidinone (1.2 l) were refluxed under stirring for 18 h. The reaction mixture was cooled, poured into water (1.0 l) and extracted with diethyl ether (2 x 1 l). The combined organic phases were washed with brine (3 x 1.5 l), dried (Na_2SO_4) and treated with activated carbon. Evaporation of the solvent gave the title compound which was crystallized from diethyl ether. Yield: 42.0 g, mp 115-118 °C.
In a corresponding manner the following indole derivatives were prepared:
5-Chloro-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **2b**, mp 162-164 °C.
3-(4-Fluorophenyl)-5-methyl-1-(4-pyridyl)-*1H*-indole **2c**, mp 125-127 °C.
5-Fluoro-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **2d**, mp 129-134 °C.
6-Chloro-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **2e**, mp 194-198 °C.
3-(4-Fluorophenyl)-1-(4-pyridyl)-5-trifluoromethyl-*1H*-indole **2f**, mp 163-165 °C.
5-Chloro-3-phenyl-1-(4-pyridyl)-*1H*-indole **2g**, mp 130-132 °C.

EXAMPLE 3

(intermediates for method a)

6-Chloro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3a**.

6-Chloro-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **2e** (1.8 g) was dissolved in acetic acid (100 ml) and PtO_2 (0.2 g) was added. After hydrogenation for 30 h at 3 ato the catalyst was filtered off, the acetic acid

was evaporated *in vacuo* and water (50 ml) was added. The acidic solution was made alkaline (pH >9) with concentrated sodium hydroxide and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were successively washed with diluted sodium hydroxide (50 ml), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave 1.5 g of the title compound as an oil.

In a corresponding manner the following indole and indazole derivatives were prepared:

3-(4-Fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3b**, (oil).

5-Chloro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3c**, (oil).

3-(4-Fluorophenyl)-5-methyl-1-(4-piperidyl)-*1H*-indole **3d**, (oil).

5-Fluoro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3e**, (oil).

3-(4-Fluorophenyl)-1-(4-piperidyl)-5-trifluoromethyl-*1H*-indole **3f**, (oil).

5-Chloro-3-phenyl-1-(4-piperidyl)-*1H*-indole **3g**, (oil).

6-Chloro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indazole **3h**, (oil).

3-(4-Fluorophenyl)-1-(4-piperidyl)-5-trifluoromethyl-*1H*-indazole **3i**, (oil).

EXAMPLE 4

(method a)

6-Chloro-3-(4-fluorophenyl)-1-[1-[2-(3-methylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole, maleate **4a**.

A mixture of 6-chloro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3a** (1.5 g), 1-(2-chloroethyl)-3-methyl-2-imidazolidinon(1.1 g), K_2CO_3 (1.0 g), KI (0.5 g) and methyl isobutyl ketone (100 ml) was refluxed for 18 h. The reaction mixture was cooled, poured into water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/isopropanol 9:1 containing 4 % triethylamine). The title compound was precipitated as its maleate from ethyl acetate. Yield: 1.4 g, mp 110-112 °C.

In a corresponding manner the following indole and indazole derivatives were prepared:

6-Chloro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4b**, mp 192-194 °C.

6-Chloro-3-(4-fluorophenyl)-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-*1H*-indole, hydrochloride, hydrate **4c**, mp 255-258 °C.

5-Chloro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4d**, mp 171-174 °C.

5-Chloro-3-(4-fluorophenyl)-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-*1H*-indole **4e**, mp 161-164 °C.

5-Chloro-3-(4-fluorophenyl)-1-[1-[2-(3-methylimidazolidin-2-on-1-yl)ethyl]-piperidyl]-*1H*-indole **4f**, mp 128-133 °C.

3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indole **4g**, mp 185-187 °C.

3-(4-Fluorophenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl)-*1H*-indole, oxalate **4h**, mp 175-177 °C.

3-(4-Fluorophenyl)-5-methyl-1-[1-[2-(3-methylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole, fumarate **4i**, mp 103-105 °C.

3-(4-Fluorophenyl)-5-methyl-1-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-*1H*-indole, oxalate **4j**, mp 120-122 °C.

3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4k**, mp 172-173 °C.

3-(4-Fluorophenyl)-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-*1H*-indole, hydrochloride, hydrate **4l**, mp 242-244 °C.

5-Fluoro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4m**, mp 153-156 °C.

5-Fluoro-3-(4-fluorophenyl)-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-*1H*-indole **4n**, mp 143-145 °C.

5-Fluoro-3-(4-fluorophenyl)-1-[1-[2-(oxazolidin-2-on-3-yl)ethyl]-4-piperidyl]-*1H*-indole **4o**, mp 123-125 °C.

5-Chloro-3-phenyl-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4p**, mp 155-157 °C.

5-Chloro-3-phenyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl)-*1H*-indole **4q**, mp 146-148 °C.

2,3-Dihydro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-fluoro-*1H*-indole **4r**, mp 182-186 °C.

3-(4-Fluorophenyl)-5-methyl-1-[1-(2-propyl)-4-piperidyl]-*1H*-indole, maleate **4s**, m p 162-163 °C.

6-Chloro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indazole **4t**, mp 195-197 °C.

3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-trifluoromethyl-*1H*-indazole **4u**, mp

217-219 °C.
3-(4-Fluorophenyl)-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-5-trifluoromethyl-*1H*-indole **4v**, mp 156-158 °C.
2-Bromo-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **4x**, mp 194-196 °C.

EXAMPLE 5

(intermediates for methods e and f)

4-[2,5-Dimethyl-3-(4-fluorophenyl)-*1H*-indol-1-yl]-1-[2-(imidazolidin-2-on-1-yl)ethyl]pyridinium iodide **5a**.

A mixture of 2,5-dimethyl-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **17a** (5.0 g) and 1-(2-iodoethyl)-2-imidazolidinon (7.6 g) and methyl isobutyl ketone (50 ml) was refluxed for 6 h. After cooling to room temperature the precipitated product was filtered off and dried *in vacuo* at 70 °C overnight. This afforded 6.3 g of the title compound, mp 215-217 °C.
In a corresponding manner the following indole derivatives were prepared:
4-[3-(4-Fluorophenyl)-5-methyl-*1H*-indol-1-yl]-1-[2-(imidazolidin-2-on-1-yl)ethyl]pyridinium iodide **5b**, mp >250 °C.
4-[3-(4-Fluorophenyl)-5-trifluoromethyl-*1H*-indol-1-yl]-1-[2-(imidazolidin-2-on-1-yl)ethyl]pyridinium iodide **5c**, mp >250 °C.

EXAMPLE 6

(method e)

2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-*1H*-indole **6a**.

4-[2,5-Dimethyl-3-(4-fluorophenyl)-*1H*-indol-1-yl]-1-[2-(imidazolidin-2-on-1-yl)ethyl]pyridinium iodide **5a** - (6.3 g) was suspended in ethanol (100 ml) and sodium borohydride (2.1 g) was added in three portions during 3.5 h. Then the solvent was evaporated *in vacuo* and water (100 ml) was added. The mixture obtained was extracted with dichloromethane (2 x 50 ml). The combined organic phases were washed with brine (100 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the title compound as an oil, which was purified by column chromatography on silica gel (eluted with ethyl acetate/ethanol 8:1 containing 4 % triethylamine). Yield: 2.5 g, mp 151-153 °C.
In a corresponding manner the following indole derivatives were prepared: 2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-*1H*-indole **6b**, mp 98-100 °C.
3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-5-methyl-*1H*-indole **6c**, mp 129-131 °C.
3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-*1H*-indole, maleate **6d**, mp 168-171 °C.
5-Chloro-2-methyl-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-phenyl-*1H*-indole, oxalate **6e**, mp 165-168 °C.
3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-5-trifluoromethyl-*1H*-indole **6f**, mp 113-115 °C.

EXAMPLE 7

(method d)

2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole **7a**.

Ammonium formate (12 g) was added in small portions during 18 h to a refluxing mixture of 2,5-dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-*1H*-indole **6a** (1.9 g), 5 % palladium on activated carbon (1 g) and ethanol (50 ml). The reaction mixture was cooled to room temperature and the solvents were evaporated *in vacuo*. After addition of water the mixture was made alkaline with concentrated NaOH and extracted with ethyl acetate (2 x 50 ml).The combined organic phases were dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. This afforded the title compound which

crystallized from diethyl ether. Yield 0.2 g, mp 188-190 °C.

In a corresponding manner the following indole derivatives were prepared:

3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-trifluoromethyl-1H-indole **7b**, mp 182-186 °C

1-[1-[2-(Imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-2-methyl-3-phenyl-*1H*-indole **7c**, mp 179-183 °C.

EXAMPLE 8

(intermediates for methods e and f)

4-[2,5-Dimethyl-3-(4-fluorophenyl)-*1H*-indol-1-yl]-1-methylpyridinium, iodide **8a**.

2,5-Dimethyl-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **17a** (5.0 g), methyl iodide (5 ml) and acetone (100 ml) were heated at 40 °C for 18 h. After cooling to room temperature the precipitated product was filtered off and dried *in vacuo* at 70 °C overnight. yield: 6.3 g, mp 217-219 °C.

In a corresponding manner the following indole derivatives were prepared:

4-(5-Chloro-2-methyl-3-phenyl-*1H*-indol-1-yl)-1-methylpyridinium iodide **8b**, mp 225-227 °C.

4-[3-(4-Fluorophenyl)-5-methyl-*1H*-indol-1-yl]-1-methylpyridinium, iodide **8c**, mp > 250 °C.

EXAMPLE 9

(method f)

2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-4-piperidyl)-*1H*-indole **9a**.

4-[2,5-Dimethyl-3-(4-fluorophenyl)-*1H*-indol-1-yl]-1-methylpyridinium, iodide **8a** (3.0 g) was dissolved in acetic acid (75 ml) and PtO_2 (0.4 g) was added. After hydrogenation for 2 weeks at 3 ato the catalyst was filtered off, the acetic acid was evaporated *in vacuo* and water (50 ml) was added. The thus obtained acidic solution was made alkaline (pH >9) with concentrated sodium hydroxide and extracted with ethyl acetate (2 x 50 ml). The organic phases were successively washed with diluted sodium hydroxide (50 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave 1.3 g of the title compound as an oil, which was purified by column chromatography on silica gel (eluted with ethyl acetate/ethanol 8:1 containing 4 % triethylamine) and crystallized from heptane. Yield 0.4 g, mp 110-112 °C.

In a corresponding manner the following indole derivative was prepared: 5-Chloro-2-methyl-3-phenyl-1-(1-methyl-4-piperidyl)-*1H*-indole **9b**, mp 131-136 °C (decomp.).

EXAMPLE 10

(intermediates for method g)

Methyl 4-[3-(4-fluorophenyl)-5-methyl-*1H*-indol-1-yl]piperidine-1-carboxylate **10a**.

A mixture of 3-(4-fluorophenyl)-5-methyl-1-(4-piperidyl)-*1H*-indole **3d** (6.0 g), K_2CO_3 (3.0 g) and dichloromethane (50 ml) was cooled to 0-5 °C and a solution of methyl chloroformate (2.2 g) in dichloromethane (50 ml) was added during 0.5 h. After reaction for further 2 h at room temperature the reaction mixture was washed with water (2 x 100 ml) and dried ($MgSO_4$). Evaporation of the solvents *in vacuo* afforded the title compound, which was used without further purification. Yield: 6.7 g, (oil). in a corresponding manner the following indole derivative was prepared:

2,2,2-Trichloroethyl-4-[3-(4-fluorophenyl)-*1H*-indol-1-yl]piperidine-1-carboxylate **10b** (oil).

EXAMPLE 11

(method g)

3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-4-piperidyl)-*1H*-indole, fumarate **11a**.

A solution of the crude methyl 4-[3-(4-fluorophenyl)-5-methyl-*1H*-indol-1-yl]piperidine-1-carboxylate **10a**, (6.7 g) in dry tetrahydrofuran (75 ml) was added to a suspension of lithium aluminum hydride (4 g) in dry

tetrahydrofuran (75 ml) during 0.5 h and the reaction mixture was refluxed for 1 h. After cooling on an ice bath water (5 ml), 6 N aqueous NaOH (5 ml) and water (10 ml) were added, succesively. The precipitate was filtered off, the filtrate was dried ($MgSO_4$) and the solvents were evaporated *in vacuo*. This afforded the title compound, as an oil, which was precipitated as its fumarate from ethanol. Yield: 1.4 g, mp 170-172 °C.

EXAMPLE 12

(intermediate for method h)

1-[1-(2-Aminoethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole **12a**.

A solution of 3-(4-fluorophenyl)-5-methyl-1-(4-piperidyl)-*1H*-indole **3d** (20 g), chloroacetonitrile (5.4 g) and triethylamine (7.5.ml) in *N*-methylpyrrolidinone (125 ml) was heated at 60 °C for 2 h. The reaction mixture was poured into ice (200 g) and extracted with diethyl ether (2 x 200 ml). The combined organic phases were washed with brine (3 x 250 ml), dried (Na_2SO_4) and the solvents evaporated *in vacuo*. This afforded the 1-[1-(2-cyanomethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, as an oil, which was used without further purification. Yield: 22.2 g. To a suspension of aluminum chloride (5.0 g) in dry diethyl ether (200 ml) was added lithium aluminum hydride (5.0 g) at 10-15 °C. Then a solution of the crude cyanomethyl compound in dry tetrahydrofuran (300 ml) was added dropwise during 0.5 h at 10-15 °C. The reaction mixture was refluxed for 2 h, cooled on an ice bath and concentrated aqueous NaOH (25 ml) was added. The inorganic salts were filtered off and the solvent evaporated *in vacuo*. The remaining oil was dissolved in dichloromethane, dried ($MgSO_4$) and the solvent was evaporated. This afforded the title compound as an oil. Yield: 18.9 g.

EXAMPLE 13

(method h)

1-[1-[2-(3,3-Dimethyl-1-thioureido)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole **13a**.

A solution of 1-[1-(2-aminoethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, **12a** (5.0 g), *N,N*-dimethylthiocarbamoylchloride (2.1 g) and triethylamine (5 ml) in dichloromethane (150 ml) was refluxed for 18 h. After cooling to room temperature the reaction mixture was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded the title compound as an oil which was purified by column chromatography on silica gel (eluted with ethyl acetate containing 4 % triethylamine). The title compound precipitated from ethyl acetate and was recrystallized from diethyl ether. Yield: 0.8 g, mp 106-108 °C.

In a corresponding manner the following indole derivative was prepared:
1-[1-[2-(3,3-Dimethyl-1-ureido)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole **13b**, mp 126-128 °C.

EXAMPLE 14

(intermediate for method h)

1-[1-(*N*-Methyl-2-aminoethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole **14a**

A mixture of 1-[1-(2-aminoethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole **12a** (8.9 g), K_2CO_3 - (4.2 g) and dichloromethane (80 ml) was cooled to 0-5 °C and a solution of methyl chloroformate (2.9 g) in dichloromethane (50 ml) was added during 15 min. After reaction for further 2 h at room temperature the reaction mixture was washed with water (2 x 50 ml), dried ($MgSO_4$) and the solvents were evaporated *in vacuo*. This afforded the 1-[1-(N-methoxycarbonyl-2-aminoethyl)-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, as an oil, which was used without further purification. Yield: 8.8 g.
A solution of the crude 1-(1-(N-methoxycarbonyl-2-aminoethyl)-4-piperidyl)-3-(4-fluorophenyl)-5-methyl-*1H*-indole (8.8 g) in dry tetrahydrofuran (75 ml) was added to a suspension of lithium aluminum hydride (2 g) in dry tetrahydrofuran (75 ml) during 15 min and the reaction mixture was refluxed for 1.5 h. After cooling on an ice bath water (4 ml), 4 N aqueous NaOH (2.5 ml) and water (10 ml) were added, succesively. The precipitate was filtered off, the solution was dried (Na_2SO_4) and the solvents were evaporated. This afforded the title compound, as an oil Yield: 6.9 g.

EXAMPLE 15

(method h)

1-[1-[2-(1,3-Dimethyl-1-ureido)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, hydrochloride **15a**.

A mixture of 1-(1-(*N*-methyl-2-aminoethyl)-4-piperidyl)-3-(4-fluorophenyl)-5-methyl-*1H*-indole **14a** (6.9), methyl isocyanate (2.1 g) and K_2CO_3 (4 g) in methyl isobutyl ketone (150 ml) was refluxed for 6 h. After cooling to room temperature water (100 ml) was added and the mixture was extracted with ethyl acetate (2 x 100 ml). The combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded the title compound as an oil which was purified by column chromatography on silica gel (eluted with ethyl acetate/ethanol 4:1, containing 4 % triethylamine). The title compound was precipitated as its hydrochloride from diethyl ether. Yield: 0.9 g, mp 88-90 °C.

EXAMPLE 16

(method j)

3-(4-Fluorophenyl)-1-[1-(2-hydroxyethyl)-4-piperidyl]-5-methyl-*1H*-indole, oxalate **16a**.

A solution of ethyl bromoacetate in acetone was added during 15 min to a mixture of 3-(4-fluorophenyl)-5-methyl-1-(4-piperidyl)-*1H*-indole **3d** (5.0 g), K_2CO_3 (2.5 g) and acetone (100 ml) at room temperature. After another 2 h the solvents were evaporated, water was added and the mixture was extracted with ethyl acetate (2 x100 ml). The combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded the crude methyl 4-[3-(4-fluorophenyl)-5-methyl-*1H*-indol-1-yl]-1-piperidinacetate (6.0 g), which was used without further purification.
A solution of the crude methyl ester (6.0 g) in tetrahydrofuran (50 ml) was added to a suspension of lithium aluminum hydride (1.2 g) in dry tetrahydrofuran (50 ml) and the mixture was refluxed for 1 h. After cooling on ice bath, water (1.5 ml) and 4 N aqueous NaOH (1.5 ml) were added. The precipitate was filtered off and the filtrate was dried (Na_2SO_4). Evaporation of the solvents afforded the title compound (4.2 g) as an oil which was purified by column chromatography on silica gel (eluted with ethyl acetate containing 4 % triethylamine). The title compound precipitated as its oxalate from acetone. Yield: 0.09 g, mp 81-83 °C.

EXAMPLE 17

2,5-Dimethyl-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indole **17a**.

2,5-Dimethyl-(4-fluorophenyl)-*1H*-indole **24a** (50 g), 4-bromopyridine, hydrochloride (80 g), K_2CO_3 (90 g), CuBr (10 g) and N-methylpyrrolidone (750 ml) were refluxed under stirring for 18 h. The reaction mixture was cooled, poured into water (1.0 l) and extracted with diethyl ether (2 x 750 ml). The combined organic phases were washed with brine (3 x 1 l), dried (Na_2SO_4) and treated with activated carbon. Evaporation of the diethyl ether afforded the title compound (29.8 g) which was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 3:1). The title compound crystallized from diethyl ether. Yield: 20.5 g, mp 172-174 °C.
In a corresponding manner the following indole and indazole derivatives were prepared:
5-Chloro-2-methyl-3-phenyl-1-(4-pyridyl)-*1H*-indole **17b**, mp 158-160 °C.
6-Chloro-3-(4-fluorophenyl)-1-(4-pyridyl)-*1H*-indazole **17c**, (oil).
3-(4-Fluorophenyl)-1-(4-pyridyl)-5-trifluoromethyl-*1H*-indazole **17d**, (oil).

EXAMPLE 18

(method c)

2,3-Dihydro-5-fluoro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **18a**

To a solution of 5-fluoro-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **3e** (2 g) in trifluoroacetic acid (30 ml) was added sodium cyanoborohydride (1 g). After 2 h reaction at room temperature the solvent was evaporated *in vacuo* and ethyl acetate (50 ml) was added. The mixture was washed twice with aqueous 2 N

sodium hydroxide (50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* afforded the crude product which was used without further purification. Yield: 1.5 g (oil).

In a corresponding manner the following indole derivative was prepared:
2,3-Dihydro-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indole **18b**, mp 180-185 °C.

EXAMPLE 19

(intermediate for method b)

1-Amino-3-(4-fluorophenyl)-5-methyl-*1H*-indole **19a**.

Potassium *tert*-butoxid (7.5 g) was added to a solution of 3-(4-fluorophenyl)-5-methyl-*1H*-indole **1c** (15 g) in DMF during 15 min at 0-5 °C. Then a suspension of potassium hydroxylamine-O-sulphonate in DMF (prepared by addition of potassium tert-butoxid (7.5 g) to a suspension of hydroxylamine-O-sulphonic acid (7.6 g) in DMF (100 ml) during 0.5 h at 0-5 °C) was added slowly at 0-5 °C. After reaction at 0 °C for 1 h the mixture was poured into ice, and extracted with diethyl ether (2 x 250 ml). The combined organic phases were washed with brine (3 x 250 ml) and dried (Na_2SO_4). Evaporation of the solvents afforded the title compound which was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:3) and crystallized from diethylether. Yield: 4.3 g, mp 116-120 °C.

EXAMPLE 20

(method b)

3-(4-Fluorophenyl)-5-methyl-1-(1-methylpiperazin-4-yl)-*1H*-indole **20a**.

To a mixture of 1-amino-3-(4-fluorophenyl)-5-methyl-*1H*-indole **19a** (1 g) and toluene (20 ml) was added a 50 % suspension of sodium amide in xylene (1.0 ml). After reaction for 15 min at room temperature a solution of *N,N*-bis(2-chloroethyl)methylamine (0.8 g) in toluene was added slowly and the mixture was refluxed for 3 h. After cooling to room temperature, the solvents were evaporated *in vacuo* and water (100 ml) was added. The mixture was extracted with ethyl acetate (2 x 50 ml) and the combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* afforded the title compound, which was purified by column chromatography on silica gel (eluted with ethyl acetate/ethanol 4:1 containing 4 % triethylamine) and crystallized from heptane. Yield: 0.5 g, mp 105-107 °C.

EXAMPLE 21

1-[1-[2-(3-Acetylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, oxalate **21a** - (Prodrug).

To a mixture of 3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indole **4g** (3 g), K_2CO_3 (1.3 g) and toluene (50 ml) was added a solution of acetyl chloride (0.6 ml) in toluene (5 ml) during 10 min at 0-5 °C. After reaction for further 18 h at room temperature the reaction mixture was filtered, the solvent was evaporated *in vacuo* and ethyl acetate (50 ml) was added. The thus formed solution was washed with brine (50 ml), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. This afforded the title compound as an oil which was purified by column chromatography on silica gel (eluted with ethyl acetate containing 4 % triethylamine). The title compound precipitated as its oxalate from acetone. Yield: 2.0 g, mp 233-235 °C.

In a corresponding manner the following indole derivative was prepared: 1-[1-[2-(3-Decanoylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole, oxalate **21b**, mp 175-176 °C.

EXAMPLE 22

Methyl 3-(4-fluorophenyl)-5-methyl-*1H*-indole-2-carboxylate **22a**.

To a solution of p-toluidine (119.4 g) in conc. aqueous HCl (575 ml) was added a solution of $NaNO_2$ - (84.6 g) in water (500 ml) at 0-5 °C during 1.5 h. The reaction mixture was added in one portion to a

mixture of methyl 2-(4-fluorobenzyl)-3-oxo-butanoate (250 g), KOH (220 g), water (0.5 l), ethanol (1.25 l) and ice (2 kg) under stirring. After reaction for 2 h at room temperature the reaction mixture was extracted with diethyl ether (2 x 2 l). The combined organic phases were washed with water (3 l) and dried (Na_2SO_4). Evaporation of the solvents afforded the crude 4-tolylhydrazone of methyl 2-oxo-3-(4-fluorophenyl)-propanoate (330 g), which was used without further purification.

A mixture of the crude hydrazone, methanol (2.25 l) and aqueous H_2SO_4 (100 ml) was refluxed for 18 h. The reaction mixture was cooled to room temperature and a part of the solvents were evaporated *in vacuo*. The thus obtained solution was cooled to 0 °C and the precipitated compound was filtered off and dried overnight *in vacuo*. at 60 °C. Yield: 180 g, mp 151-155 °C.

In a corresponding manner the following indole derivatives were prepared: Methyl 5-chloro-3-(4-fluorophenyl)-*1H*-indole-2-carboxylate **22b**, mp 184-186 °C.

Methyl 5-fluoro-3-(4-fluorophenyl)-*1H*-indole-2-carboxylate, **22c**, (oil).

Methyl 3-(4-fluorophenyl)-*1H*-indole-2-carboxylate **22d**, mp 148-150 °C.

Methyl 3-(4-fluorophenyl)-5-trifluoromethyl-*1H*-indole-2-carboxylate **22e**, mp 136-139 °C.

Methyl 5-chloro-3-phenyl-*1H*-indole-2-carboxylate **22f**, (oil).

EXAMPLE 23

Methyl 6-chloro-3-(4-fluorophenyl)-*1H*-indole-2-carboxylate **23a**.

To a mixture of a 50 % sodium hydride suspension in mineral oil (52.5 g) (which was extracted with dry heptane) and dry tetrahydrofuran (250 ml) was added a solution of N-benzoyl 5-chloro-2-(4-fluorobenzoyl)-aniline (129 g) in dry tetrahydrofuran (500 ml) during 0.5 h at 20 °C (ice bath). After 1 h methyl 2-bromoacetate (101 ml) was added during 0.5 h at 20 °C (ice bath) and the mixture was stirred for another 1 hour. The solvents were evaporated *in vacuo*. The remaining oil was diluted with methanol (250 ml) and 5.4 M sodium methoxide in methanol (670 ml) was added carefully. After 1 h at room temperature the solvents were evaporated *in vacuo* and water (0.5 l) was added. The thus obtained mixture was extracted with ethyl acetate (2 x 0.75 l) and the combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of the solvents *in vacuo* afforded the title compound, which was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:3) and crystallized from heptane. Yield: 33 g, mp 172-183 °C.

EXAMPLE 24

2,5-Dimethyl-3-(4-fluorophenyl)-*1H*-indole **24a**.

A solution of 4-fluorophenylacetone (60 g), 4-tolylhydrazine, HCl (68.8 g) and triethylamine (165 ml) in ethanol (600 ml) was refluxed for 18 h. The reaction mixture was cooled to room temperature, the solvents were evaporated *in vacuo* and water (500 ml) was added to the remaining oil. The thus obtained mixture was extracted with ethyl acetate (2 x 250 ml). The combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of the solvents afforded the crude 4-fluorophenylacetone tolylhydrazone (100 g) as an oil, which was used without further purification.

The crude hydrazone (100 g), ethanol (700 ml) and conc. aqueous H_2SO_4 (40 ml) were refluxed for 18 h. After cooling to room temperature water (0.5 l) was added. The thus obtained mixture was extracted with (2 x 700 ml) ethyl acetate and the combined organic phases were washed with brine, dried and the solvents were evaporated *in vacuo*. This afforded the title compound, which was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:4) and crystallized from heptane. Yield: 75.5 g, mp:124-128 °C.

In a corresponding manner the following indole derivative was prepared: 5-Chloro-3-phenyl-2-methyl-*1H*-indole **24b**, (oil).

EXAMPLE 25

6-Chloro-3-(4-fluorophenyl)-*1H*-indazole **25a**.

To solution of 5-chloro-2-(4-fluorobenzoyl)aniline (5 g) in 6 M aqueous HCl (25 ml) was added a solution of $NaNO_2$ (2.5 g) in water (5 ml) at 0-5 °C under stirring during 15 min. After stirring for further 0.5 h at 0 °C a solution of $SnCl_2$ (20 g) in conc. aqueous HCl (25 ml) was added. The reaction mixture was allowed to

heat to room temperature and after 0.5 h the precipitate was filtered off and suspended in 2 N aqueous NaOH. The suspension was filtered and dichloromethane was added to the precipitate. The thus obtained solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvents afforded the title compound (2.5 g) as an oil which was used without further purification.

In a corresponding manner the following indazole derivative was prepared: 3-(4-Fluorophenyl)-5-trifluoromethyl-*1H*-indazole **25b**, (oil)

EXAMPLE 26

2-Bromo-3-(4-fluorophenyl)-1-(4-piperidyl)-*1H*-indole **26a**.

A mixture of 2,2,2-trichloroethyl 4-[3-(4-fluorophenyl)-*1H*-indol-1-yl]piperidine-1-carboxylate **10b** (4.0 g), N-bromosuccinimid (1.5 g) and tetrachloromethane (60 ml) was refluxed for 2 h. The reaction mixture was cooled to room temperature and the precipitate was filtered off. Evaporation of the solvent afforded the crude 2,2,2-trichloroethyl 2-bromo-4-[3-(4-fluorophenyl)-*1H*-indol-1-yl]piperidine-1-carboxylate (4.4 g) as an oil which was used without further purification. A mixture of the crude 2-bromo-indole (4.4 g), zinc powder (4.4 g) and 90 % acetic acid in water (150 ml) was heated at 40 °C for 30 min. The reaction mixture was filtered and the solvent evaporated *in vacuo*. To the remaining oil was added ethyl acetate (50 ml) and the thus obtained solution was washed successively with water, 4 N aqueous NaOH and brine. Evaporation of the solvents afforded the title compound as an oil (2.9 g).

EXAMPLE 27

2-Chloro-3-(4-fluorophenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl]-*1H*-indole **27a.**

A mixture of 3-(4-Fluorophenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl)-*1H*-indole **4h** (3.0 g), dimethylsulphoxide (0.51 g) and conc. aqueous HCl (1 ml) was heated to 60 °C for 0.5 h under stirring. The reaction mixture was cooled to room temperature and water was added. The solution was extracted with ethyl acetate (2 x 50 ml). The combined organic phases were washed with 4 N aqueous NaOH and brine. Evaporation of the solvent gave an oil which was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:3). This afforded the title compound which crystallized from diethyl ether. Yield 0.4 g, mp 127-130 °C.

PHARMACOLOGICAL TESTS

The compounds of the invention were tested in well recognized and reliable methods. The tests were as follows and the results are given in the following Table 1. The well known $5HT_2$ antagonists ritanserin and ICI 169369 were included in the tests for comparison purposes.

INHIBITION OF ^{3}H-KETANSERIN BINDING TO SEROTONIN S_2

($5\text{-}HT_2$) RECEPTORS IN RAT CORTEX *IN VITRO*

By this method the inhibition by drugs of the binding of ^{3}H-Ketanserin (0,5 nM) to Serotonin S_2 ($5\text{-}HT_2$) receptors in membranes from rat is determined *in vitro*. Method in Hyttel, *Pharmacology & Toxicology*, *61*, 126-129, 1987.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed and cortical tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM tris buffer pH 7.7 (at 25 °C). The centrifuge glassware used in this step has been rinsed by sonication for 10 min. in ethanol. The homogenate is centrifuged twice at 20,000 g for 10 min. at 4 °C with rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 500 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 2000 µl of tissue suspension (final tissue content corresponds to 4 mg original tissue). The binding experiment is initiated by addition of 100 µl of ^{3}H-Ketanserin (final concentration 0.5 nM) and by

placing the tubes in a 37 °C water bath. After incubation for 30 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor ™ 15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 1 µM mianserin.

For determination of the inhibiiton of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 1 µM mianserin.

^{3}H-Ketanserin = [ethylene-^{3}H]-ketanserin hydrochloride from New England Nuclear, specific activity 60-80 Ci/mmol).

INHIBITION OF ^{3}H-SPIPERONE BINDING TO DOPAMINE D-2 RECEPTORS IN RAT CORPUS STRIATUM *IN VITRO*

By this method the inhibition by drugs of the binding of ^{3}H-spiperone (=^{3}H-spiroperidol) (0.5 nM) to dopamine D-2 receptors in membranes from rat corpus striatum is determined *in vitro*. Method and results in Hyttel & Larsen, J. *Neurochem*, *44*, 1615-1622, 1985).

Procedure

Male Wistar (Mol:Wistar) rats (125-250 g) are sacrificed and striatal tissue is dissected and weighed. The tissue is homogenized (Ultra Turrax, 10 sec.) in 10 ml of ice-cold 50 mM K-phosphate buffer pH 7.4 (at 25 °C). The homogenate is centrifuged twice at 20,000 g for 10 min. at 4 °C wtih rehomogenization of the pellet in 10 ml ice-cold buffer. The final pellet is homogenized in 1300 vol (w/v) ice-cold buffer.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 4000 µl of tissue suspension (final tissue content corresponds to 3.08 mg original tissue). The binding experimental is initiated by addition of 100 µl of ^{3}H-spiperone (final concentration 0.5 nM) and by placing the tubes in a 37 °C water bath. After incubation for 10 min. the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice-cold buffer which are then poured on the filters. Thereafter, the filters are washed with 2 x 5 ml of buffer. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor ™ 15) are added. After shaking for 1 h and storage 2 hrs in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 10 µM of 6,7-ADTN.

For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper and the best fitting S-shaped curve is drawn. The IC_{50} value is determined as the concentration at which the binding is 50% of the total binding in control samples minus the nonspecific binding in the presence of 10 µM of 6,7-ADTN.
^{3}H-Spiperone = [phenyl-4-^{3}H]-spiperone from Amersham international plc. England, specific activity 15-25 Ci/mmol.

TABEL 1

Compound	^{3}H-Ketanserin Binding IC_{50} nM	^{3}H-Spiroperidol Binding IC_{50} nM
4a	1.5	46
4b	1.9	37
4c	3.7	42
4d	5.7	410
4e	5.4	570
4f	1.4	550
4g	1.6	920
4h	2.7	1100
4i	1.4	680
4j	4.5	1200
4k	3.1	120
4l	3.3	74
4m	3.2	250
4n	3.1	190
4o	37	790
4p	29	2800
4q	25	3000
4r	3.4	230
4s	12	330
4t	38	1900
4u	220	42000
4v	11	>1000
4x	11	650
6a	2.8	6300
6b	3.8	710
6c	1.4	320
6d	4.4	32
6e	9.4	1000
6f	3.6	440
7a	3.4	6900

TABEL 1 (continued)

Compound	^{3}H-Ketanserin Binding IC_{50} nM	^{3}H-Spiroperidol Binding IC_{50} nM
7b	6.2	>1000
7c	7.8	5300
9a	5.3	2600
9b	17	2900
11a	4.5	540
13a	3.7	250
13b	2.3	260
15a	1.8	>1000
16a	22	1500
18b	4.3	1100
20a	13	3900
21a	18	890
27a	10	3200
Ritanserin	0.4	12
ICI 169369	15.0	490

It is seen from the table that the derivatives of the present invention which have been tested are all selective 5-HT_2 ligands, the affinity for the 5-HT_2 receptor as shown in the ^{3}H-ketanserin binding test being very high as compared to the affinity for the dopamine D-2 receptor as measured in the ^{3}H-spiroperidol binding test. As compared to the known standard 5-HT_2 antagonists ritanserin and ICI 169369 the compounds of the invention are in general found to be more selective.

Additionally the compounds of the invention were tested in the following well known and reliable *in vivo tests* :

QUIPAZINE INHIBITION

Quipazine is a 5-HT_2 agonist, which induces head twitches in rats. The test is a test for 5-HT_2-antagonistic effect testing the ability to inhibit head twitches. The method and test results for some reference substances are published by Arnt et al. (*Drug Development Research, 16*, 59-70, 1989).

ANTAGONISM OF PERGOLIDE-INDUCED CIRCLING BEHAVIOUR IN RATS WITH UNILATERAL 6-OHDA LESIONS

Dopamine D-2 agonists induce contralateral circling behaviour in rats with 6-OHDA lesions. Pergolide-induced circling is antagonized by dopamine D-2 antagonists. (Arnt,J. and J.Hyttel, *Eur. J. Pharmacol. 102*, 349-354, 1984; Arnt, J. and J. Hyttel, *J. Neural. Transm. 67*, 225-240, 1986). The test is an extremely sensitive test for dopamine D-2 antagonism *in vivo*.

These *in vivo* tests showed that the compounds of the invention are strong and selective 5-HT_2 antagonists with long duration of action *in vivo* (Quipazine test) and that they are substantially without

dopamine D-2 antagonistic activity *in vivo* as shown in the test for antagonism of pergolide induced circling.

Accordingly, the compounds of the present invention are selective 5-HT_2 antagonist *in vivo* and *in vitro* thus being useful in the treatment of anxiety, depression, sleep disturbances, migraine, negative symptoms of schizophrenia, and Parkinson's Disease without neurological side effects as known from the classical neuroleptics.

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5 milligrams of Compound 4c calculated as the free base:

Comp. **4c**	5 mg
Lactose	18 mg
Potato starch	27 mg
Sucrose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of Compound 4b calculated as the free base:

Comp. **4b**	50 mg
Lactose	16 mg
Potato starch	45 mg
Sucrose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

Comp. **4h**	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

Comp. **4c**	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

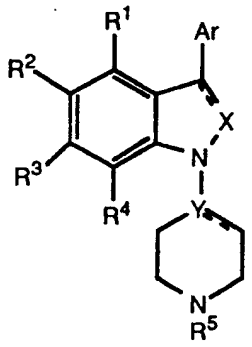
5) Solution for injection containing per milliliter:

Comp. **4h**	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. An 3-arylindole or 3-arylindazole derivative having formula :

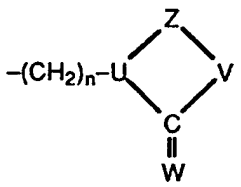


I

wherein Ar is phenyl optionally substituted with one or more substituents selected from halogen, hydroxy, trifluoromethyl, and cyano, or Ar is 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

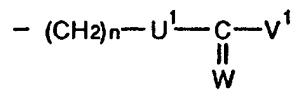
R^1-R^4 are independently selected from hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulphonyl, cyano, trifluoromethyl, or trifluoromethylthio;

the dotted line emanating from X in the ring system designates an optional bond; when said dotted line indicates a bond, X is nitrogen or a group CR^6 wherein R^6 is hydrogen, halogen, trifluoromethyl or C_1-C_4 alkyl;
when the dotted line indicates no bond, X is CH_2 ;
the dotted line, emanating from the Y, indicates an optional bond;
when it does not indicate a bond Y is N or CH; and when it indicates a bond Y is C; R^5 is hydrogen or C_1-C_4 alkyl, optionally substituted with one or two hydroxy groups, or R^5 is a group taken from structures **1a** and **1b** :



1a.

or

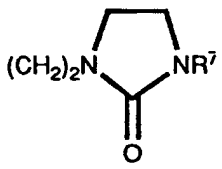


1b.

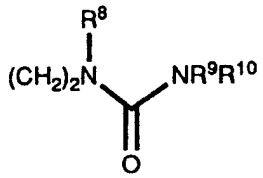
wherein n is an integer from 2 - 6;
W is oxygen, or sulphur;
U is nitrogen or CH;
Z is $-(CH_2)_m-$, m being 2 or 3, or Z is 1,2-phenylene optionally substituted with halogen or trifluoromethyl or Z is -CH=CH- , $-COCH_2-$ or $-CSCH_2-$;
V is oxygen, CH_2, or NR^7 , wherein R^7 is hydrogen or C_1-C_4 alkyl or C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl(C_1-C_4)alkyl optionally substituted with one or two hydroxy groups;
U^1 is a group NR^8,wherein R^8 is hydrogen or C_1-C_4 alkyl or C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl(C_1-C_4)alkyl optionally substituted with one or two hydroxy groups; and
V^1 is NR^9R^{10}, where each of R^9 and R^{10} may be independently selected among the R^8-substituents;
provided that R^5 may not be methyl when R^1-R^4 each are hydrogen, X and Y are CH, and Ar is phenyl;
and pharmaceutically acceptable acid addition salts and prodrugs thereof.

2. A derivative according to claim 1, **characterized in** that Ar is phenyl optionally substituted with halogen, preferably 4-fluorophenyl.

3. A derivative according to any of claims 1 or 2 **characterized in** that R^5 is a group of the formula



or



where R^7, R^8, R^9 and R^{10} independently are selected from hydrogen, C_1-C_4 alkyl and C_2-C_4 alkenyl.

4. A derivative according to any of the previous claims, **characterized in** that X is CR^6.

5. A derivative according to claim 4, **characterized in** that R^2 and/or R^6 are other than hydrogen.

6. A derivative according to any of the previous claims, **characterized in** that R^2 is selected from halogen, $-CH_3$, and $-CF_3$ and/or R^3 is selected from hydrogen, halogen, $-CH_3$, and $-CF_3$.

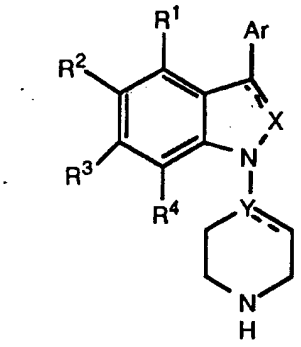
7. A derivative according to claim 1, **characteriz d in** that it is: 5-Chloro-3-(4-fluorophenyl)-1-[1-[2-(3-methylimidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole,
3-(4-Fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indole,
3-(4-Fluorophenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl]ethyl]-4-piperidyl)-*1H*-indole,

2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-*1H*-indole,
2,5-Dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indole,
2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-4-piperidyl)-*1H*-indole, or 1-[1-[2-(1,3-Dimethyl-1-ureido)-ethyl]-4-piperidyl]-3-(4-fluorophenyl)-5-methyl-*1H*-indole.

8. A pharmaceutical preparation **characterized in** that it comprises a compound of any of the claims 1 - 7 or a pharmaceutically acceptable salt or a prodrug thereof as an active ingredient together with a pharmaceutically acceptable carrier or diluent.

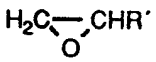
9. Use of a derivative of any of claims 1 - 7 or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the therapeutical treatment of anxiety, agression, negative symptoms of schizophrenia, depression, migraine, sleep disturbances, drug-induced Parkinsonism or Parkinsons disease.

10. A method for the preparation of a derivative of claim 1 comprising
a) reacting a compound of the following formula:

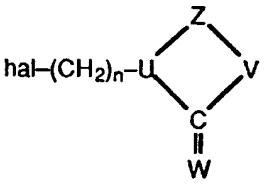


II

wherein R^1, R^2, R^3, R^4, X, Y, Ar and the dotted lines are as defined above, with a C_1-C_4 alkyl halide, alkyl mesylate or tosylate, with an epoxide of the formula

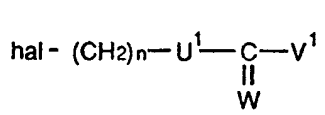


wherein R' is hydrogen, methyl or ethyl or with a halide of the general formula



III a

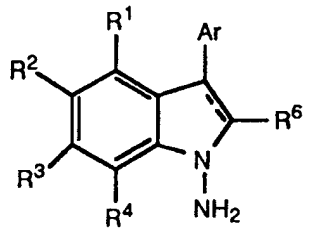
or



III b

wherein n, W, U, V, Z, V^1 and U^1 are as defined above;

b) reacting a compound of following formula:

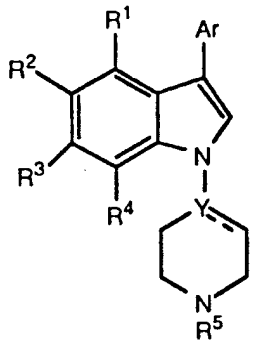


IV

wherein R^1, R^2, R^3, R^4, R^6, Ar and the dotted line are as defined above, with a compound of the general formula

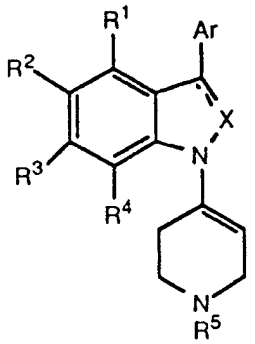
$R^5N(CH_2CH_2hal)_2$ V

in which R^5 is as defined above and hal is halogen;
c) reducing the indole ring of a compound of the general formula



VI

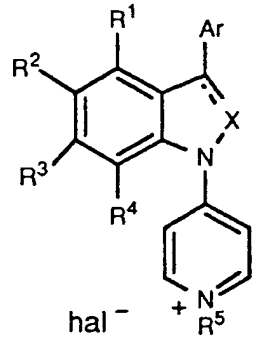
wherein R^1-R^5, Ar, Y and the dotted line are as defined above, to a dihydroindole ring;
d) reducing the double bond in the tetrahydropyridyl ring in a compound of the formula:



VII

wherein R^1 - R^5, X, Ar and the dotted line are as defined above;

e) reducing the pyridinium ring in a compound of following formula:

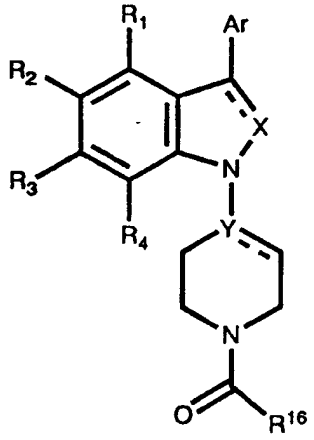


VIII

wherein R^1 - R^5, X, Ar and the dotted line are as defined above except that R^5 may not be hydrogen, and hal is halogen, to a tetrahydropyridine ring;

f) reducing the pyridinium ring in a compound of the above Formula **VIII** or the pyridyl ring of a compound of formula **XIV** to a piperidine ring;

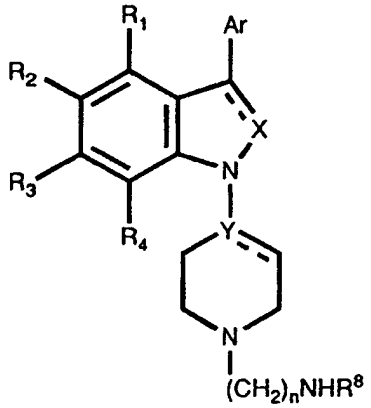
g) reducing the carbonyl group of a compound of the following formula :



IX

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined and R^{16} is hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

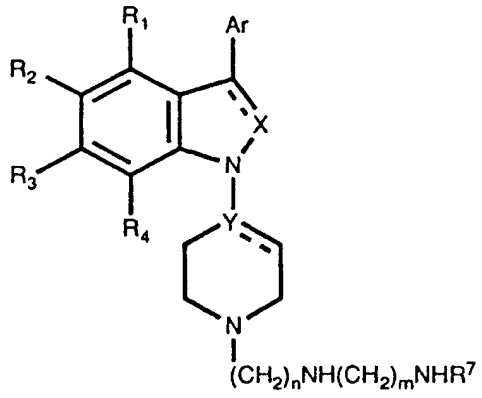
h) acylating an aminoalkyl derivative of the following formula :



X

wherein R^1 - R^4, X, Y, Ar, R^8, n and the dotted lines are as defined above, with an acylating agent such as a carboxylic acid halogenide, anhydride or mixed anhydride, or a carbamyl or thiocarbamyl chloride, an isocyanate, isothiocyanate, or a substituted chloroformate;

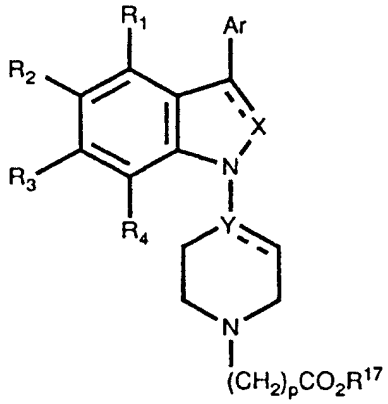
i) ringclosure reaction of an intermediate ethylene or propylene diamine derivative of the following formula :



XI

wherein R^1 - R^4, R^8, n, X, Y, Ar and the dotted lines are as defined above and m is 2 or 3, with phosgene, thiophosgene or carbondisulphide to form a substituent of the structure **1a** ; or

j) reducing a carboxylic acid or carboxylic acid derivative of the following formula :



XII

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined, R^{17} is hydrogen or lower alkyl and p is 1, 2 or 3 ;

and then, if desired:

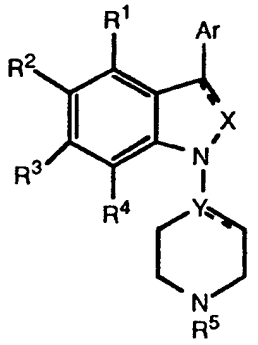
acylating a compound prepared in one of the methods (a) to (j) having the formula **I** in which R^5 is a structure **1a** or **1b** wherein V is NH, or V^1 is NHR^{10} or U^1 is NH with an acylating agent, or esterifying an available hydroxy group in a compound of formula **I** in order to obtain a prodrug;

converting a compound prepared in one of methods (a) to (j) in a pharmaceutically acceptable acid addition salt thereof; or

resolving an optically active compound of formula **I** prepared in one of methods (a) to (j) in optically active isomers thereof.

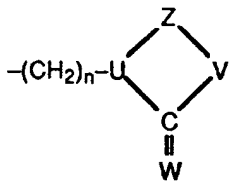
Claim for the following Contracting States : ES, GR

1. A method for the preparation of an 3-arylindole or 3-arylindazole derivative having formula :



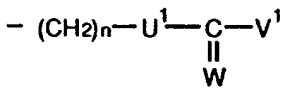
I

wherein Ar is phenyl optionally substituted with one or more substituents selected from halogen, hydroxy, trifluoromethyl, and cyano, or Ar is 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;
R^1-R^4 are independently selected from hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulphonyl, cyano, trifluoromethyl, or trifluoromethylthio;
the dotted line emanating from X in the ring system designates an optional bond; when said dotted line indicates a bond, X is nitrogen or a group CR^6 wherein R^6 is hydrogen, halogen, trifluoromethyl or C_1-C_4 alkyl;
when the dotted line indicates no bond, X is CH_2 ;
the dotted line, emanating from the Y, indicates an optional bond;
when it does not indicate a bond Y is N or CH; and when it indicates a bond Y is C; R^5 is hydrogen or C_1-C_4 alkyl, optionally substituted with one or two hydroxy groups, or R^5 is a group taken from structures **1a** and **1b** :



1a.

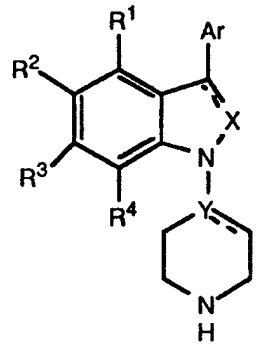
or



1b.

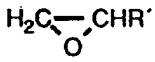
wherein n is an integer from 2 - 6;
W is oxygen, or sulphur;
U is nitrogen or CH ;
Z is $-(CH_2)_m-$, m being 2 or 3, or Z is 1,2-phenylene optionally substituted with halogen or trifluoromethyl or Z is -CH = CH- , $-COCH_2-$ or $-CSCH_2-$;
V is oxygen, CH_2, or NR^7, wherein R^7 is hydrogen or C_1-C_4 alkyl or C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl(C_1-C_4)alkyl optionally substituted with one or two hydroxy groups;
U^1 is a group NR^8,wherein R^8 is hydrogen or C_1-C_4 alkyl or C_2-C_4 alkenyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl(C_1-C_4)alkyl optionally substituted with one or two hydroxy groups; and
V^1 is NR^9R^{10}, where each of R^9 and R^{10} may be independently selected among the R^8-substituents;
provided that R^5 may not be methyl when R^1-R^4 each are hydrogen, X and Y are CH, and Ar is phenyl;
or a pharmaceutically acceptable acid addition salt or prodrug thereof comprising

a) reacting a compound of the following formula:

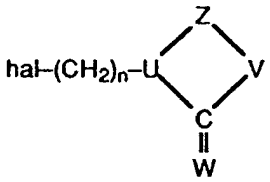


II

wherein R^1, R^2, R^3, R^4, X, Y, Ar and the dotted lines are as defined above, with a C_1-C_4 alkyl halide, alkyl mesylate or tosylate, with an epoxide of the formula

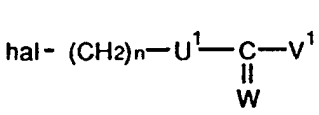


wherein R' is hydrogen, methyl or ethyl or with a halide of the general formula



III a

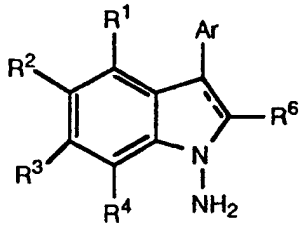
or



III b

wherein n, W, U, V, Z, V^1 and U^1 are as defined above;

b) reacting a compound of following formula:



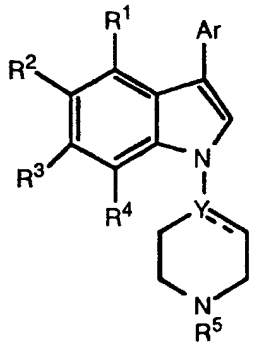
IV

wherein R^1, R^2, R^3, R^4, R^6, Ar and the dotted line are as defined above, with a compound of the general formula

$R^5N(CH_2CH_2hal)_2$ V

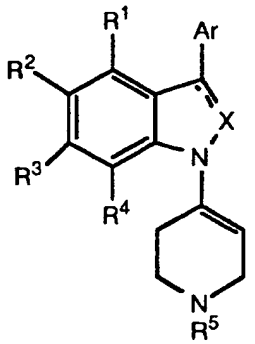
in which R^5 is as defined above and hal is halogen;

c) reducing the indole ring of a compound of the general formula



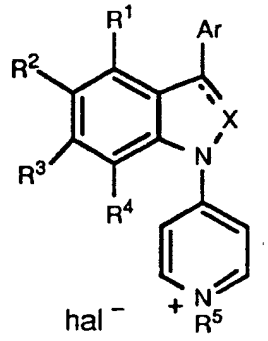
VI

wherein R^1-R^5, Ar, Y and the dotted line are as defined above, to a dihydroindole ring;
d) reducing the double bond in the tetrahydropyridyl ring in a compound of the formula:



VII

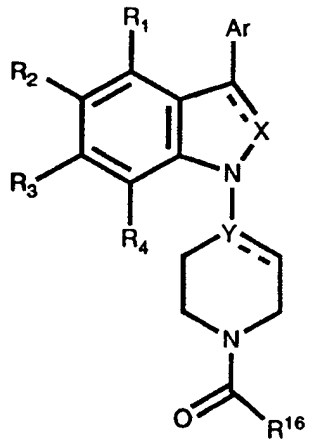
wherein R^1 - R^5, X, Ar and the dotted line are as defined above;
e) reducing the pyridinium ring in a compound of following formula:



VIII

wherein R^1 - R^5, X, Ar and the dotted line are as defined above except that R^5 may not be hydrogen, and hal is halogen, to a tetrahydropyridine ring;
f) reducing the pyridinium ring in a compound of the above Formula **VIII** or the pyridyl ring of a compound of formula **XIV** to a piperidine ring;

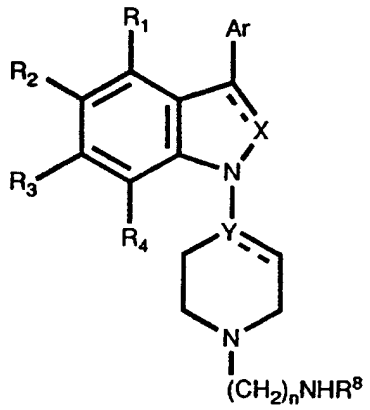
g) reducing the carbonyl group of a compound of the following formula :



IX

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined and R^{16} is hydrogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

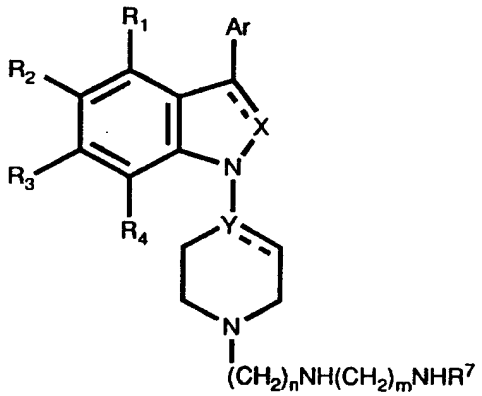
h) acylating an aminoalkyl derivative of the following formula :



X

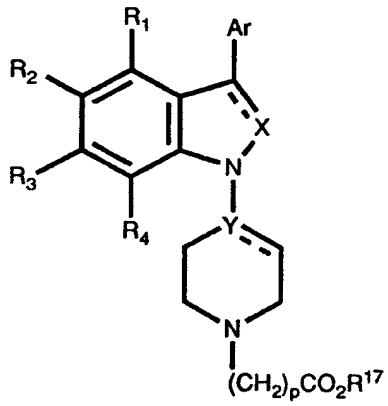
wherein R^1 - R^4, X, Y, Ar, R^8, n and the dotted lines are as defined above, with an acylating agent such as a carboxylic acid halogenide, anhydride or mixed anhydride, or a carbamyl or thiocarbamyl chloride, an isocyanate, isothiocyanate, or a substituted chloroformate;

i) ringclosure reaction of an intermediate ethylene or propylene diamine derivative of the following formula :



XI

wherein R^1 - R^4, R^8, n, X, Y, Ar and the dotted lines are as defined above and m is 2 or 3, with phosgene, thiophosgene or carbondisulphide to form a substituent of the structure **1a** ; or
j) reducing a carboxylic acid or carboxylic acid derivative of the following formula :

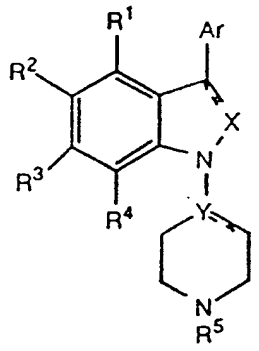


XII

wherein R^1 - R^4, X, Y, Ar and the dotted lines are as previously defined, R^{17} is hydrogen or C_1-C_4 alkyl and p is 1, 2 or 3 ;
and then, if desired:
acylating a compound prepared in one of the methods (a) to (j) having the formula **I** in which R^5 is a structure **1a** or **1b** wherein V is NH, or V^1 is NHR^{10} or U^1 is NH with an acylating agent, or esterifying an available hydroxy group in a compound of formula **I** in order to obtain a prodrug;
converting a compound prepared in one of methods (a) to (j) in a pharmaceutically acceptable acid addition salt thereof; or
resolving an optically active compound of formula **I** prepared in one of methods (a) to (j) in optically active isomers thereof.

Pat ntansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Ein Arylindol oder 3-Arylindazolderivat mit folgender Formel:



I

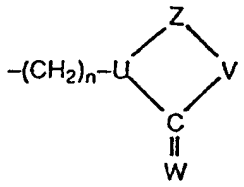
worin Ar eine Phenylgruppe ist, gegebenenfalls substituiert mit einem oder mehreren Substituenten ausgewählt aus Halogen, Hydroxy, Trifluormethyl und Cyan, oder Ar ist 2-Thienyl, 3-Thienyl, 2-Furyl, 3-Furyl, 2-Pyridyl, 3-Pyridyl, oder 4-Pyridyl.

R^1-R^4 sind unabhängig ausgewählt aus Wasserstoff, Halogen, C_1-C_4 Alkyl, C_1-C_4 Alkoxy, C_1-C_4 Alkylthio, C_1-C_4 Alkylsulphonyl, Cyan, Trifluormethyl, oder Trifluormethylthio;

die von X ausgehende gestrichelte Linie im Ringsystem deutet gegebenenfalls eine Bindung an; wenn die besagte gestrichelte Linie eine Bindung bezeichnet, dann ist X Stickstoff oder eine Gruppe CR^6, worin R^6 Wasserstoff, Halogen, Trifluormethyl oder C_1-C_4 Alkyl ist; wenn die gestrichelte Linie keine Bindung ist, dann ist X gleich CH_2;

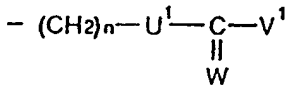
die von Y ausgehende gestrichelte Linie, bedeutet gegebenenfalls eine Bindung; wenn sie keine Bindung anzeigt ist Y gleich N oder CH; wenn sie eine Bindung anzeigt, ist Y gleich C;

R^5 ist Wasserstoff oder C_1-C_4 Alkyl, gegebenenfalls substituiert mit einer oder zwei Hydroxygruppen, oder R^5 wird aus den Strukturen **1a** und **1b** genommen.



1a.

oder



1b.

worin n eine ganze Zahl von 2-6 ist;

W ist Sauerstoff, oder Schwefel;

U ist Stickstoff oder CH;

Z ist $-(CH_2)_m-$, wobei m 2 oder 3 ist, oder Z ist ein 1,2-Phenylen wahlweise substituiert mit Halogen oder Trifluormethyl, oder Z ist -CH=CH-, $-COCH_2-$ oder $-CSCH_2-$;

V ist Sauerstoff, CH_2, oder NR^7, worin R^7 Wasserstoff ist oder C_1-C_4 Alkyl oder C_2-C_4 Alkenyl, C_3-C_8 Cycloalkyl oder C_3-C_8 Cycloalkyl(C_1-C_4) Alkyl gegebenenfalls mit einer oder zwei Hydroxygruppen substituiert;

U^1 ist eine Gruppe NR^8, worin R^8 ein Wasserstoff ist, oder C_1-C_4 Alkyl oder C_2-C_4 Alkenyl, C_3-C_8 Cycloalkyl oder C_3-C_8 Cycloalkyl(C_1-C_4) Alkyl gegebenenfalls mit einer oder zwei Hydroxygruppen substituiert; und

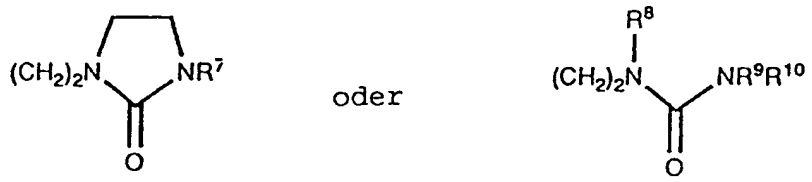
V^1 ist NR^9R^{10}, wo jede der R^9 und R^{10} Gruppen unabhängig voneinander aus den R^8-Substituenten ausgewählt werden können;

vorrausgesetzt daß, wenn R^1-R^4 jeweils Wasserstoff sind, X und Y gleich CH sind, und Ar eine

Phenylgruppe ist, R^5 nicht Methyl sein kann;
und pharmazeutisch annehmbare Säureadditionssalze und Medikamentenvorstufen derselben.

2. Derivat gemäß Anspruch 1, dadurch gekennzeichnet, daß Ar Phenyl ist, gegebenenfalls mit Halogen substituiert, vorzugsweise 4-Fluorphenyl.

3. Derivat gemäß irgeneiner der Ansprüche 1 oder 2 dadurch gekennzeichnet, daß R^5 eine Gruppe der folgenden Formel ist



worin R^7, R^8, R^9 und R^{10} unabhängig aus Wasserstoff, C_1-C_4 Alkyl oder C_2-C_4 Alkenyl ausgewählt sind.

4. Derivat gemäß irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß X gleich CR^6 ist.

5. Derivat gemäß Anspruch 4, dadurch gekennzeichnet, daß R^2 und/oder R^6 etwas anderes als Wasserstoff sind.

6. Derivat gemäß einem beliebigen der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß R^2 aus Halogen, $-CH_3$, und $-CF_3$ ausgewählt ist und/oder R^3 ist ausgewählt aus Halogen, $-CH_3$, und $-CF_3$.

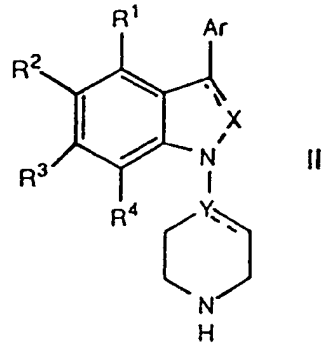
7. Derivat gemäß Anspruch 1, dadurch gekennzeichnet, daß dieses ist:
5-Chlor-3-(4-fluorphenyl)-1-[1-[2-(3-methyl-imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indol,
3-(4-Fluorphenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-5-methyl-*1H*-indol,
3-(4-Fluorphenyl)-5-methyl-1-[1-[2-[3-(2-propyl)imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indol,
2,5-Dimethyl-3-(4-fluorphenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4yl]-*1H*-indol,
2,5-Dimethyl-3-(4-fluorphenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-4-piperidyl]-*1H*-indol,
2,5-Dimethyl-3-(4-fluorphenyl)-1-(1-methyl-4-piperidyl-*1H*-indol, oder
1[1-[2-(1,3-Dimethyl-1-ureid)ethyl]-4-piperidyl]-3-(4-fluorphenyl)-5-methyl-*1H*-indol.

8. Pharmazeutische Zubereitung dadurch gekennzeichnet, daß sie eine Verbindung gemäß irgendeiner der Ansprüche 1-7, oder ein pharmazeutisch annehmbares Salz oder eine Medikamentenvorstufe derselben als aktiver Bestandteil umfasst, zusammen mit einem pharmazeutisch annehmbaren Täger oder Verdünnungsmittel.

9. Verwendung eines Derivates gemäß irgendeinem der Ansprüche 1-7 oder eines pharmazeutisch annehmbaren Salzes oder eine Medikamentenvorstufe derselben, zur Herstellung eines Medikaments für die therapeutische Behandlung von Angstzuständen, Aggressivität, negativen Symptomen von Schizophrenie, Depression, Migräne, Schlafstörungen, Pharmainduzierter Parkinsonismus oder Parkinsonscher Krankheit.

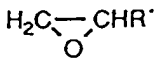
10. Verfahren zur Herstellung eines Derivates gemäß Anspruch 1, umfassend

a) zur Reaktion bringen einer Verbindung folgender Formel:

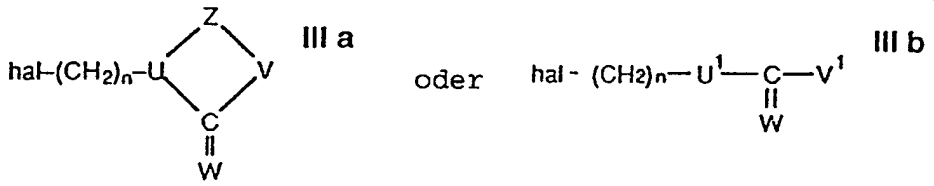


II

worin R^1, R^2, R^3, R^4, X, Y, Ar und die gestrichelten Linien wie oben definiert sind, mit einem C_1-C_4 Alkylhalogenid, Alkylmesylat oder Tosylat, mit einem Epoxid der Formel



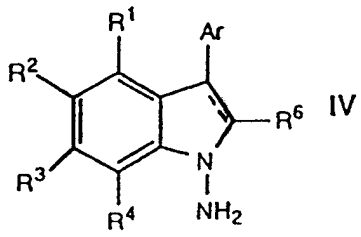
worin R' Wasserstoff, Methyl oder Ethyl oder ein Halogenid der allgemeinen Formel



III a oder III b

ist, worin n, W, U, V, Z, V^1, und U^1 wie oben definiert sind;

b) zur Reaktion bringen einer Verbindung folgender Formel:



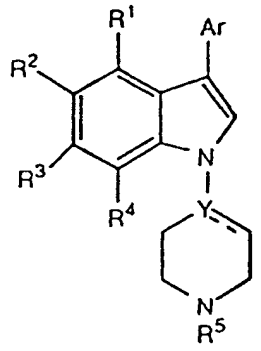
IV

worin R^1, R^2, R^3, R^4,R^6, Ar und die gestrichelten Linien wie oben definiert sind, mit einer Verbindung der allgemeinen Formel

$R^5N(CH_2CH_2hal)_2$ **V**

in der R^5 wie oben definiert ist und hal ist Halogen;

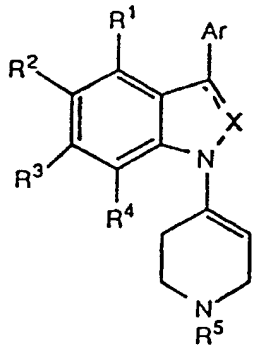
c) Reduzieren des Indolrings einer Verbindung der allgemeinen Formel



VI

worin R^1-R^5, Ar, Y und die gestrichelten Linien wie oben definiert sind, zu einem Dihydroindolring;

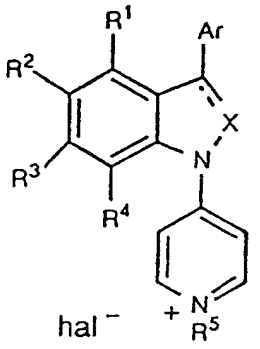
d) Reduzieren der Doppelbindung im Tetrahydropyridylring in einer Verbindung der Formel:



VII

worin R^1-R^5, X, Ar und die gestrichelten Linien wie oben definiert sind,

e) Reduzieren des Pyridiniumrings in einer Verbindung der folgenden Formel:

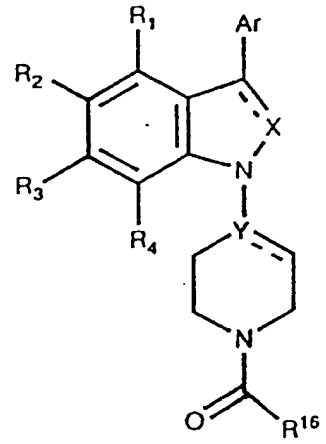


VIII

worin R^1-R^5, X, Ar und die gestrichelten Linien wie oben definiert sind, mit Ausnahme daß R^5 nicht Wasserstoff sein kann, und hal ist Halogen, zum Tetrahydropyridinring;

f) Reduzieren des Pyridiniumrings in einer Verbindung der obigen Formel **VIII** oder der Pyridylring einer Verbindung der Formel **XIV** zu einem Piperidinring;

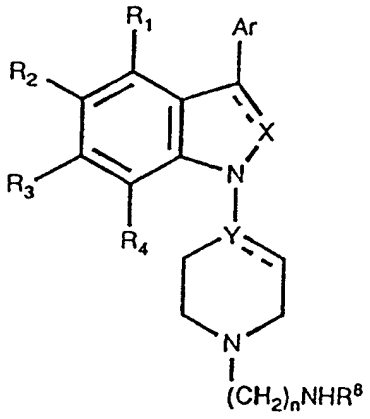
g) Reduzieren der Carbonylgruppe einer Verbindung der folgenden Formel:



IX

worin R^1-R^4, X, Y, Ar und die gestrichelten Linien wie vorher definiert sind und R^{16} ist Wasserstoff, C_1-C_4 Alkyl oder C_1-C_4 Alkoxy;

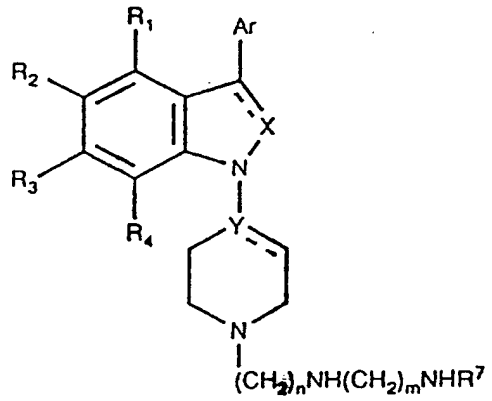
h) Acylieren eines Aminoalkylderivates der folgenden Formel:



X

worin R^1-R^4, X, Y, Ar, R^8, n und die gestrichelten Linien wie oben definiert sind, mit einem Acylierungsreagenz wie einem Carbonsäurehalogenid, Anhydrid oder einen gemischten Anhydrid, oder einem Harnstoff- oder Thioharnstoffehlorid, einem Isocyanat, Isothiocyanat, oder einem substituierten Chlorkohlensäureester.

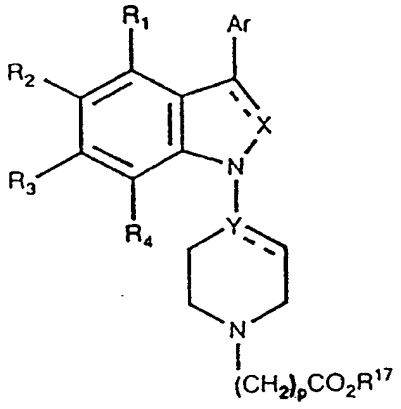
i) Ringschlußreaktion eines intermediären Ethylen- oder Propylendiamißderivates der folgenden Formel:



XI

worin R^1-R^4, R^8, n, X, Y, Ar und die gestrichelten Linien wie oben definiert sind und m 2 oder 3 ist, mit Phosgen, Thiophosgen oder Kohlenstoffdisulfid zur Bildung eines Substituenten der Struktur **1a**; oder

j) Reduzieren einer Carbonsäure oder eines Carbonsäurederivates der folgenden Formel:



XII

worin R^1-R^4, X, Y, Ar und die gestrichelten Linien wie oben definiert sind, R^{17} ist Wasserstoff oder ein niedriger Alkylrest und p ist 1, 2, oder 3;

und dann, wenn gewünscht:

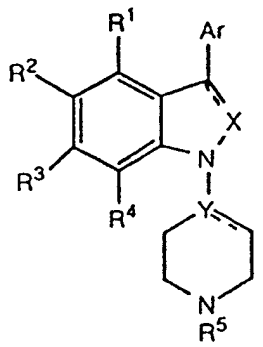
Acylieren einer gemäß, einem der Verfahren (a) bis (j) hergestellten Verbindung der Formel **I**, in der R^5 einer Struktur **1a** oder **1b** entspricht, worin V gleich NH, oder V^1 gleich NHR^{10} ist, oder U^1 gleich NH ist, mit einem Acylierungsreagenz, oder Veresterung einer verfügbaren Hydroxygruppe in einer Verbindung der Formel **I** um eine Medikamentenvorstufe zu erhalten;

Umwandlung einer, nach Methoden (a) bis (j) hergestellten Verbindung, in ein pharmazeutisch annehmbares Säureadditionssalze derselben; oder

Auflösung einer optisch aktiven Verbindung der Formel **I**, hergestellt nach einer der Verfahren (a) bis (j) in optisch aktive Isomere derselben.

Patentanspruch für folgende Vertragsstaaten : ES, GR

1. Ein Verfahren zur Herstellung eines Arylindol- oder 3-Arylindazolderivates mit folgender Formel:



I

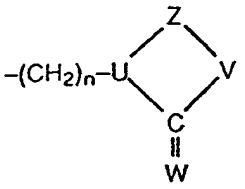
worin Ar eine Phenylgruppe ist, gegebenenfalls substituiert mit einem oder mehreren Substituenten ausgewählt aus Halogen, Hydroxy, Trifluormethyl und Cyan, oder Ar ist 2-Thienyl, 3-Thienyl, 2-Furyl, 3-Furyl, 2-Pyridyl, 3-Pyridyl, oder 4-Pyridyl.

R^1-R^4 sind unabhängig ausgewählt aus Wasserstoff, Halogen, C_1-C_4 Alkyl, C_1-C_4 Alkoxy, C_1-C_4 Alkylthio, C_1-C_4 Alkylsulphonyl, Cyan, Trifluormethyl, oder Trifluormethylthio;

die von X ausgehende gestrichelte Linie im Ringsystem deutet gegebenenfalls eine Bindung an; wenn die besagte gestrichelte Linie eine Bindung bezeichnet, dann ist X Stickstoff oder eine Gruppe CR^6, worin R^6 Wasserstoff, Halogen, Trifluormethyl oder C_1-C_4 Alkyl ist; wenn die gestrichelte Linie keine Bindung ist, dann ist X gleich CH_2;

die von Y ausgehende gestrichelte Linie, bedeutet gegebenenfalls eine Bindung; wenn sie keine Bindung anzeigt ist Y gleich N oder CH; wenn sie eine Bindung anzeigt, ist Y gleich C;

R^5 ist Wasserstoff oder C_1-C_4 Alkyl, gegebenenfalls substituiert mit einer oder zwei Hydroxygruppen, oder R^5 wird aus den Strukturen **1a** und **1b** genommen.



1a.

oder

1b.

worin n eine ganze Zahl von 2-6 ist;

W ist Sauerstoff, oder Schwefel;

U ist Stickstoff oder CH;

Z ist $-(CH_2)_m-$, wobei m 2 oder 3 ist, oder Z ist ein 1,2-Phenylen wahlweise substituiert mit Halogen oder Trifluormethyl, oder Z ist -CH=CH-, $-COCH_2-$ oder $-CSCH_2-$;

V ist Sauerstoff, CH_2, oder NR^7, worin R^7 Wasserstoff ist oder C_1-C_4 Alkyl oder C_2-C_4 Alkenyl, C_3-C_8 Cycloalkyl oder C_3-C_8 Cycloalkyl(C_1-C_4) Alkyl gegebenenfalls mit einer oder zwei Hydroxygruppen substituiert;

U^1 ist eine Gruppe NR^8, worin R^8 ein Wasserstoff ist, oder C_1-C_4 Alkyl oder C_2-C_4 Alkenyl, C_3-C_8 Cycloalkyl oder C_3-C_8 Cycloalkyl(C_1-C_4) Alkyl gegebenenfalls mit einer oder zwei Hydroxygruppen substituiert; und

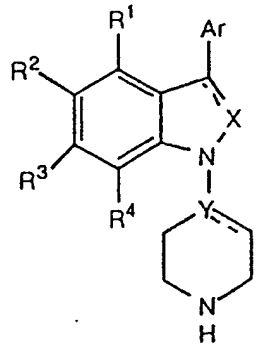
V^1 ist NR^9R^{10}, wo jede der R^9 und R^{10} Gruppen unabhängig voneinander aus den R^8-Substituenten ausgewählt werden können;

vorrausgesetzt daß, wenn R^1-R^4 jeweils Wasserstoff sind, X und Y gleich CH sind, und Ar eine Phenylgruppe ist, R^5 nicht Methyl sein kann;

oder ein pharmazeutisch annehmbares Säureadditionssalz oder Medikamentenvorstufe derselben,

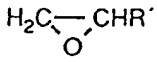
umfassend:

a) zur Reaktion bringen einer Verbindung folgender Formel:

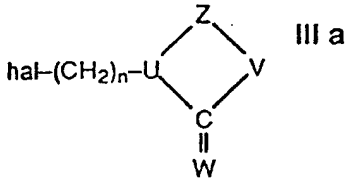


II

worin R^1, R^2, R^3, R^4, X, Y, Ar und die gestrichelten Linien wie oben definiert sind, mit einem C_1-C_4 Alkylhalogenid, Alkylmesylat oder Tosylat, mit einem Epoxid der Formel

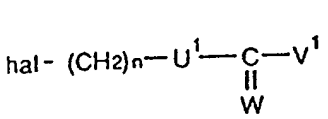


worin R' Wasserstoff, Methyl oder Ethyl oder ein Halogenid der allgemeinen Formel



III a

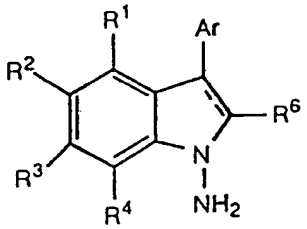
oder



III b

ist, worin n, W, U, V, Z, V^1, und U^1 wie oben definiert sind;

b) zur Reaktion bringen einer Verbindung folgender Formel:



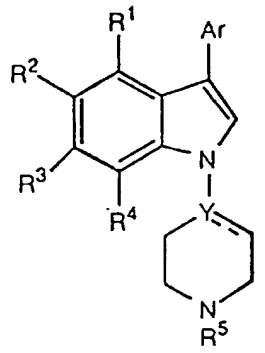
IV

worin R^1, R^2, R^3, R^4,R^6, Ar und die gestrichelten Linien wie oben definiert sind, mit einer Verbindung der allgemeinen Formel

$R^5N(CH_2CH_2hal)_2$ V

in der R^5 wie oben definiert ist und hal ist Halogen;

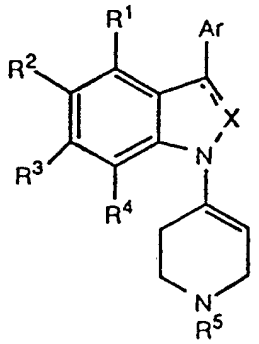
c) Reduzieren des Indolrings einer Verbindung der allgemeinen Formel



VI

worin R^1-R^5, Ar, Y und die gestrichelten Linien wie oben definiert sind, zu einem Dihydroindolring;

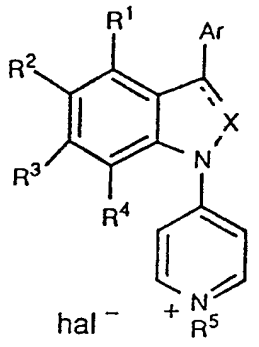
d) Reduzieren der Doppelbindung im Tetrahydropyridylring in einer Verbindung der Formel:



VII

worin R^1-R^5, X, Ar und die gestrichelten Linien wie oben definiert sind;

e) Reduzieren des Pyridiniumrings in einer Verbindung der folgenden Formel:

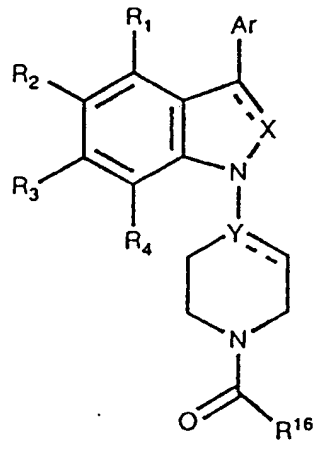


VIII

worin R^1-R^5, X, Ar und die gestrichelten Linien wie oben definiert sind, mit Ausnahme daß R^5 nicht Wasserstoff sein kann, und hal ist Halogen, zum Tetrahydropyridinring;

f) Reduzieren des Pyridiniumrings in einer Verbindung der obigen Formel **VIII** oder der Pyridylring einer Verbindung der Formel **XIV** zu einem Piperidinring;

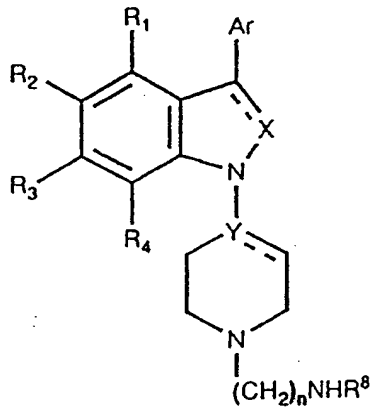
g) Reduzieren der Carbonylgruppe einer Verbindung der folgenden Formel:



IX

worin R^1-R^4, X, Y, Ar und die gestrichelten Linien wie vorher definiert sind und R^{16} ist Wasserstoff, C_1-C_4 Alkyl oder C_1-C_4 Alkoxy;

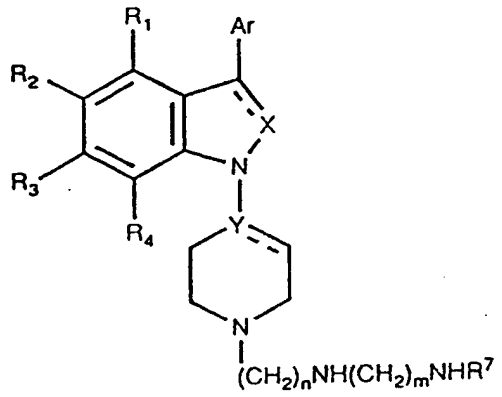
h) Acylieren eines Aminoalkylderivates der folgenden Formel:



X

worin R^1-R^4, X, Y, Ar, R^8, n und die gestrichelten Linien wie oben definiert sind, mit einem Acylierungsreagenz wie einem Carbonsäurehalogenid, Anhydrid oder einem gemischten Anhydrid, oder einem Harnstoff- oder Thioharnstoffchlorid, einem Isocyanat, Isothiocyanat, oder einem substituierten Chlorkohlensäureester.

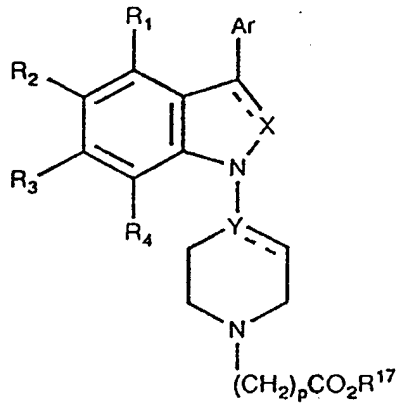
i) Ringschlußreaktion eines intermediären Ethylen- oder Propylendiaminderivates der folgenden Formel:



XI

worin R^1-R^4, R^8, n, X, Y, Ar und die gestrichelten Linien wie oben definiert sind und m 2 oder 3 ist, mit Phosgen, Thiophosgen oder Kohlenstoffdisulfid zur Bildung eines Substituenten der Struktur **1a**; oder

j) Reduzieren einer Carbonsäure oder eines Carbonsäurederivates der folgenden Formel:



XII

worin R^1-R^4, X, Y, Ar und die gestrichelten Linien wie oben definiert sind, R^{17} ist Wasserstoff oder ein niedriger Alkylrest und p ist 1, 2, oder 3;

und dann, wenn gewünscht:

Acylieren einer gemäß, einem der Verfahren (a) bis (j) hergestellten Verbindung der Formel **I**, in der R^5 einer Struktur **1a** oder **1b** entspricht, worin V gleich NH, oder V^1 gleich NHR^{10} ist, oder U^1 gleich NH ist, mit einem Acylierungsreagenz, oder Veresterung einer verfügbaren Hydroxygruppe in einer Verbindung der Formel **I** um eine Medikamentenvorstufe zu erhalten;

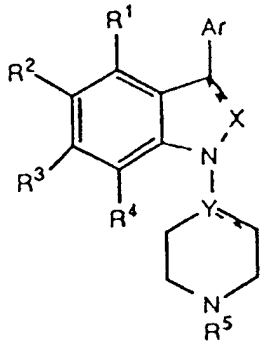
Umwandlung einer, nach Methoden (a) bis (j) hergestellten Verbindung, in ein pharmozeutisch annehmbares Säureadditionssalze derselben; oder

Auflösung einer optisch aktiven Verbindung der Formel **I**, hergestellt nach einer der Verfahren (a) bis (j) in optisch aktive Isomere derselben.

R vendications

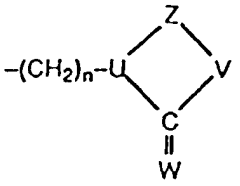
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Un dérivé de 3-arylindole ou de 3-arylindazole de formule :



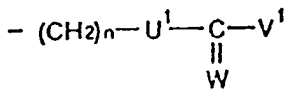
I

dans laquelle Ar est un phényle facultativement substitué avec un ou plusieurs substituants choisis parmi un halogène, un hydroxy, un trifluorométhyle et un cyano, ou Ar est un 2-thiényle, un 3-thiényle, un 2-furyle, un 3-furyle, un 2-pyridyle, un 3-pyridyle ou un 4-pyridyle ;
R^1 à R^4 sont indépendamment choisis parmi un hydrogène, un halogène, un alkyle en C_1-C_4, un alcoxy en C_1-C_4, un alkylthio en C_1-C_4, un alkylsulfonyle en C_1-C_4, un cyano, un trifluorométhyle ou un trifluorométhylthio ;
le pointillé partant de X dans le système cyclique indique une liaison facultative ; lorsque ledit pointillé indique une liaison, X est un azote ou un groupe CR^6 dans lequel R^6 est un hydrogène, un halogène, un trifluorométhyle ou un alkyle en C_1-C_4 ;
lorsque le pointillé n'indique pas de liaison, X est CH_2 ;
le pointillé partant de Y indique une liaison facultative ;
lorsqu'il n'indique pas une liaison, Y est N ou CH ; et lorsqu'il indique une liaison, Y est C ;
R^5 est un hydrogène ou un alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ou R^5 est un groupe choisi parmi les structures 1a et 1b :



1a.

ou



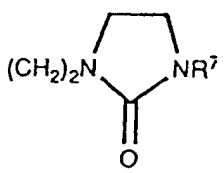
1b.

où n est un entier de 2 à 6 ;
W est un oxygène ou un soufre ;
U est un azote ou CH ;
Z est $-(CH_2)_m-$, m étant 2 ou 3, ou Z est un 1,2-phénylène facultativenent substitué avec un halogène ou un trifluorométhyle, ou Z est -CH=CH-, $-COCH_2$- ou $-CSCH_2$- ;
V est un oxygène, CH_2 ou NR^7, où R^7 est un hydrogène ou un alkyle en C_1-C_4 ou un alcényle en C_2-C_4, un cycloalkyle en C_3-C_8 ou un (cycloalkyl en C_3-C_8)alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ;
U^1 est un groupe NR^8 dans lequel R^8 est un hydrogène ou un alkyle en C_1-C_4 ou un alcényle en C_2-C_4, un cycloalkyle en C_3-C_8 ou un (cycloalkyl en C_3-C_8)alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ; et
V^1 est NR^9R^{10} où chacun de R^9 et de R^{10} peut être indépendamment choisi parmi les substituants R^8 ;
sous réserve que R^5 ne puisse pas être un méthyle lorsque R^1 à R^4 sont chacun un hydrogène, X et Y sont CH et Ar est un phényle ;
et les sels d'addition d'acides pharmaceutiquement acceptables et les précurseurs de médicament

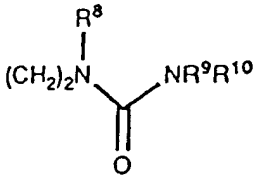
correspondants.

2. Un dérivé selon la revendication 1, caractérisé en ce que Ar est un phényle facultativement substitué avec un halogène, de préférence un 4-fluorophényle.

3. Un dérivé selon l'une quelconque des revendications 1 ou 2, caractérisé en ce que R^5 est un groupe de formule :



ou



où R^7, R^8, R^9 et R^{10} sont choisis indépendamment parmi un hydrogène, un alkyle en C_1-C_4 et un alcényle en C_2-C_4.

4. Un dérivé selon l'une quelconque des revendications précédentes, caractérisé en ce que X est CR^6.

5. Un dérivé selon la revendication 4, caractérisé en ce que R^2 et/ou R^6 sont autres qu'un hydrogène.

6. Un dérivé selon l'une quelconque des revendications précédentes, caractérisé en ce que R^2 est choisi parmi un halogène, $-CH_3$ et $-CF_3$ et/ou R^3 est choisi parmi un hydrogène, un halogène, $-CH_3$ et $-CF_3$.

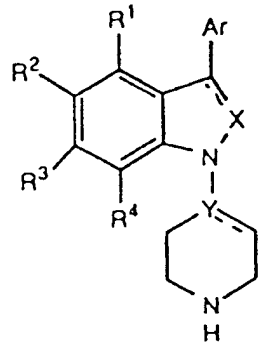
7. Un dérivé selon la revendication 1, caractérisé en ce qu'il est :
le 5-chloro-3-(4-fluorophényl)-1-[1-[2-(3-méthylimidazolidine-2-one-1-yl)éthyl]-4-pipéridyl]-1H-indole,
le 3-(4-fluorophényl)-1-[1-[2-(imidazolidine-2-one-1-yl)éthyl]-4-pipéridyl]-5-méthyl-1H-indole,
le 3-(4-fluorophényl)-5-méthyl-1-[1-[2-[3-(2-propyl)imidazolidine-2-one-1-yl]éthyl]-4-pipéridyl]-1H-indole,
le 2,5-diméthyl-3-(4-fluorophényl)-1-[1-[2-(imidazolidine-2-one-1-yl) éthyl]-1,2,3,6-tétrahydropyridine-4-yl]-1H-indole,
le 2,5-diméthyl-3-(4-fluorophényl)-1-[1-[2-(imidazolidine-2-one-1-yl) éthyl]-4-pipéridyl]-1H-indole,
le 2,5-diméthyl-3-(4-fluorophényl)-1-(1-méthyl-4-pipéridyl)-1H-indole ou
le 1-[1-[2-(1,3-diméthyl-1-uréido)éthyl]-4-pipéridyl]-3-(4-fluorophényl)-5-méthyl-1H-indole.

8. Une préparation pharmaceutique, caractérisée en ce qu'elle comprend un composé de l'une quelconque des revendications 1 à 7 ou un sel pharmaceutiquement acceptable ou un précurseur de médicament correspondants, en tant qu'ingrédient actif avec un véhicule ou diluant pharmaceutiquement acceptables.

9. Utilisation d'un dérivé de l'une quelconque des revendications 1 à 7 ou d'un sel pharmaceutiquement acceptable ou d'un précurseur de médicament correspondants pour la préparation d'un médicament pour le traitement thérapeutique de l'anxiété, de l'agression, des symptômes négatifs de la schizophrénie, de la dépression, de la migraine, des troubles du sommeil, du syndrome parkinsonien médicamenteux ou de la maladie de Parkinson.

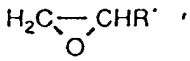
10. Un procédé pour la préparation d'un dérivé de la revendication 1 comprenant :

a) la réaction d'un composé de formule suivante :

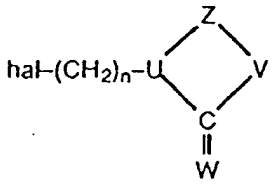


II

dans laquelle R^1, R^2, R^3, R^4, X, Y, Ar et les pointillés sont tels que définis ci-dessus, avec un halogénure d'alkyle en C_1-C_4, un mésylate d'alkyle ou un tosylate, avec un époxyde de formule

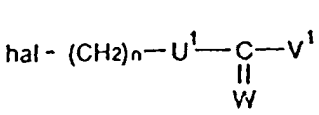


dans laquelle R' est un hydrogène, un méthyle ou un éthyle, ou avec un halogénure de formule générale



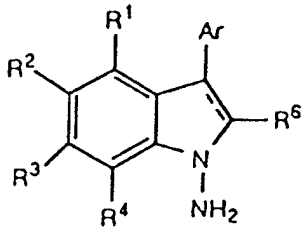
III a

ou



III b

où n, W, U, V, Z, V^1 et U^1 sont tels que définis ci-dessus ;
b) la réaction d'un composé de formule suivante :



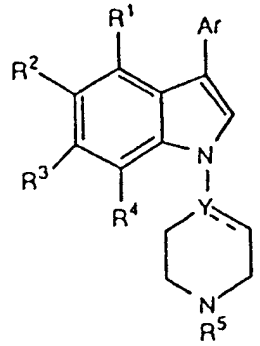
IV

dans laquelle R^1, R^2, R^3, R^4, R^6, Ar et le pointillé sont tels que définis ci-dessus, avec un composé de formule générale

$R^5N(CH_2CH_2hal)_2$ V

dans laquelle R^5 est tel que défini ci-dessus et hal est un halogène ;

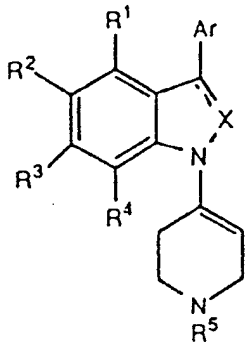
c) la réduction du cycle indole d'un composé de formule générale



VI

dans laquelle R^1 à R^5, Ar, Y et le pointillé sont tels que définis ci-dessus, en un cycle dihydro-indole ;

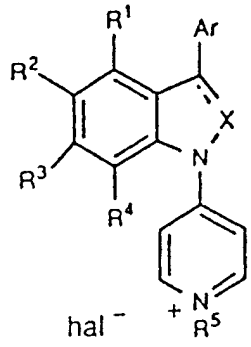
d) la réduction de la double liaison du cycle tétrahydropyridyle d'un composé de formule :



VII

dans laquelle R^1 à R^5, X, Ar et le pointillé sont tels que définis ci-dessus ;

e) la réduction du cycle pyridinium d'un composé de formule suivante :

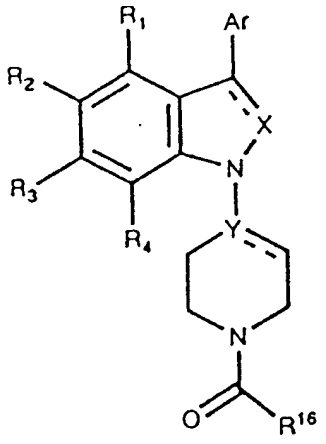


VIII

dans laquelle R^1 à R^5, X, Ar et le pointillé sont tels que définis ci-dessus, si ce n'est que R^5 ne peut pas être un hydrogène, et hal est un halogène, en cycle tétrahydropyridine ;

f) la réduction du cycle pyridinium d'un composé de formule VIII ci-dessus ou du cycle pyridyle d'un composé de formule XIV en un cycle pipéridine ;

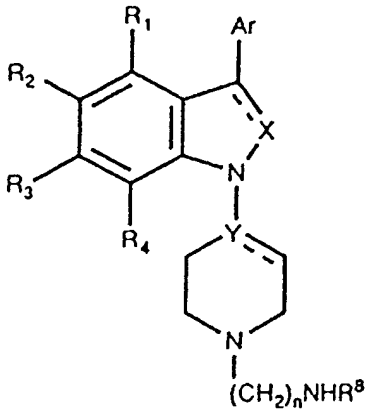
g) la réduction du groupe carbonyle d'un composé de formule suivante :



IX

dans laquelle R^1 à R^4, X, Y, Ar et les pointillés sont tels que précédemment définis et R^{16} est un hydrogène, un alkyle en C_1-C_4 ou un alcoxy en C_1-C_4 ;

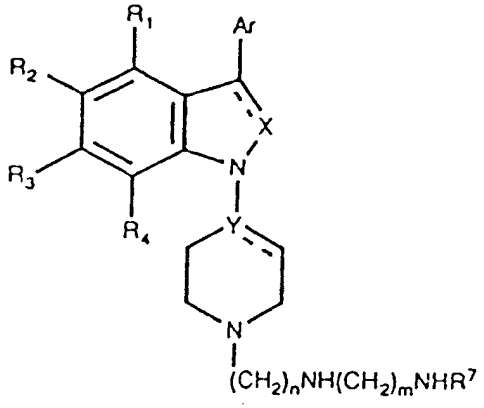
h) l'acylation d'un dérivé d'aminoalkyle de formule suivante :



X

dans laquelle R^1 à R^4, X, Y, Ar, R^8, n et les pointillés sont tels que définis ci-dessus, avec un agent d'acylation tel qu'un halogénure, un anhydride ou un anhydride mixte d'acide carboxylique, ou un chlorure de carbamyle ou de thiocarbamyle, un isocyanate, un isothiocyanate ou un chloroformiate substitué ;

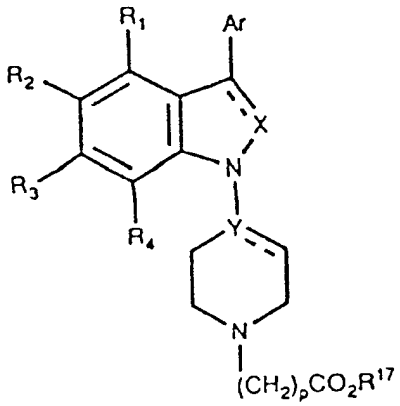
i) la réaction de cyclisation d'un dérivé intermédiaire d'éthylène-ou de propylène-diamine de formule suivante :



XI

dans laquelle R^1 à R^4, R^8, n, X, Y, Ar et les pointillés sont tels que définis ci-dessus et m est 2 ou 3, avec le phosgène, le thiophosgène ou le disulfure de carbone, pour former un substituant de structure 1a ; ou

j) la réduction d'un acide carboxylique ou d'un dérivé d'acide carboxylique de formule suivante :



XII

dans laquelle R^1 à R^4, X, Y, Ar et les pointillés sont tels que précédemment définis, R^{17} est un hydrogène ou un alkyle inférieur et p est 1, 2 ou 3 ;

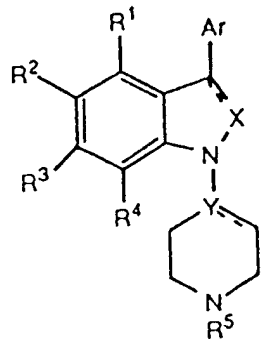
puis, si on le désire :

l'acylation d'un composé préparé dans l'un des procédés (a) à (j) répondant à la formule I dans laquelle R^5 est une structure 1a ou 1b lorsque V est NH, ou V^1 est NHR^{10}, ou U^1 est NH, avec un agent d'acylation, ou l'estérification d'un groupe hydroxy disponible dans un composé de formule I pour obtenir un précurseur de médicament ; la conversion d'un composé préparé selon l'un des procédés (a) à (j) en un sel d'addition d'acide pharmaceutiquement acceptable correspondant ; ou

le dédoublement d'un composé optiquement actif de formule I, préparé selon l'un des procédés (a) à (j), en ses isomères optiquement actifs.

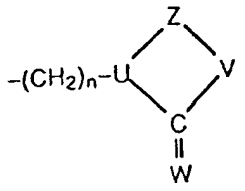
Revendication pour les Etats contractants suivants : ES, GR

1. Un procédé pour la préparation d'un dérivé de 3-arylindole ou de 3-arylindazole de formule :



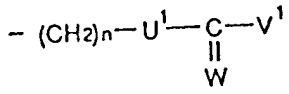
I

dans laquelle Ar est un phényle facultativenent substitué avec un ou plusieurs substituants choisis parmi un halogène, un hydroxy, un trifluorométhyle et un cyano, ou Ar est un 2-thiényle, un 3-thiényle, un 2-furyle, un 3-furyle, un 2-pyridyle, un 3-pyridyle ou un 4-pyridyle ;
R^1 à R^4 sont indépendamment choisis parmi un hydrogène, un halogène, un alkyle en C_1-C_4, un alcoxy en C_1-C_4, un alkylthio en C_1-C_4, un alkylsulfonyle en C_1-C_4, un cyano, un trifluorométhyle ou un trifluorométhylthio ;
le pointillé partant de X dans le système cyclique indique une liaison facultative ; lorsque ledit pointillé indique une liaison, X est un azote ou un groupe CR^6 dans lequel R^6 est un hydrogène, un halogène, un trifluorométhyle ou un alkyle en C_1-C_4 ;
lorsque le pointillé n'indique pas de liaison, X est CH_2 ;
le pointillé partant de Y indique une liaison facultative ;
lorsqu'il n'indique pas une liaison, Y est N ou CH ; et lorsqu'il indique une liaison, Y est C ;
R^5 est un hydrogène ou un alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ou R^5 est un groupe choisi parmi les structures 1a et 1b :



1a.

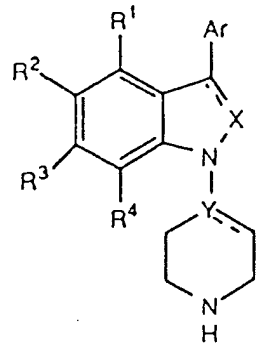
ou



1b.

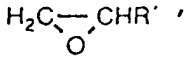
où n est un entier de 2 à 6 ;
W est un oxygène ou un soufre ;
U est un azote ou CH ;
Z est $-(CH_2)_m-$, m étant 2 ou 3, ou Z est un 1,2-phénylène
facultativement substitué avec un halogène ou un trifluorométhyle, ou Z est -CH=CH-, $-COCH_2$- ou $-CSCH_2$- ;
V est un oxygène, CH_2 ou NR^7, où R^7 est un hydrogène ou un alkyle en C_1-C_4 ou un alcényle en C_2-C_4, un cycloalkyle en C_3-C_8 ou un (cycloalkyl en C_3-C_8)alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ;
U^1 est un groupe NR^8 dans lequel R^8 est un hydrogène ou un alkyle en C_1-C_4 ou un alcényle en C_2-C_4, un cycloalkyle en C_3-C_8 ou un (cycloalkyl en C_3-C_8)alkyle en C_1-C_4 facultativement substitué avec un ou deux groupes hydroxy ; et
V^1 est NR^9R^{10} où chacun de R^9 et de R^{10} peut être indépendamment choisi parmi les substituants R^8 ;
sous réserve que R^5 ne puisse pas être un méthyle lorsque R^1 à R^4 sont chacun un hydrogène, X et Y sont CH et Ar est un phényle ;
ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou d'un précurseur de médicament correspondants, comprenant

a) la réaction d'un composé de formule suivante :

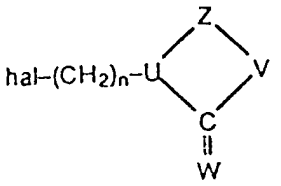


II

dans laquelle R^1, R^2, R^3, R^4, X, Y, Ar et les pointillés sont tels que définis ci-dessus, avec un halogénure d'alkyle en C_1-C_4, un mésylate d'alkyle ou un tosylate, avec un époxyde de formule

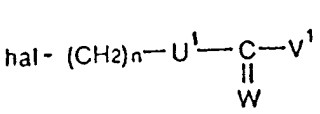


dans laquelle R' est un hydrogène, un méthyle ou un éthyle, ou avec un halogénure de formule générale



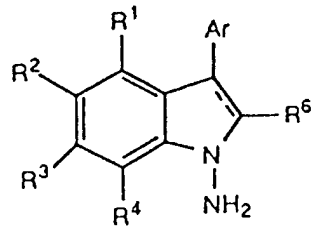
III a

ou



III b

où n, W, U, V, Z, V^1 et U^1 sont tels que définis ci-dessus ;
b) la réaction d'un composé de formule suivante :



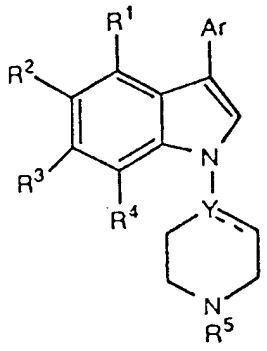
IV

dans laquelle R^1, R^2, R^3, R^4, R^6, Ar et le pointillé sont tels que définis ci-dessus, avec un composé de formule générale

$R^5N(CH_2CH_2hal)_2$ V

dans laquelle R^5 est tel que défini ci-dessus et hal est un halogène ;

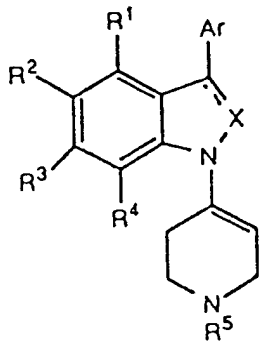
c) la réduction du cycle indole d'un composé de formule générale



VI

dans laquelle R^1 à R^5, Ar, Y et le pointillé sont tels que définis ci-dessus, en un cycle dihydro-indole ;

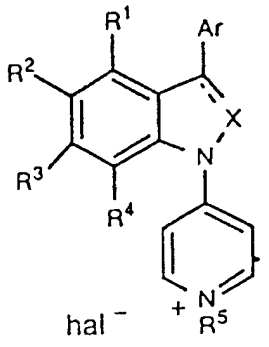
d) la réduction de la double liaison du cycle tétrahydropyridyle d'un composé de formule :



VII

dans laquelle R^1 à R^5, X, Ar et le pointillé sont tels que définis ci-dessus ;

e) la réduction du cycle pyridinium d'un composé de formule suivante :

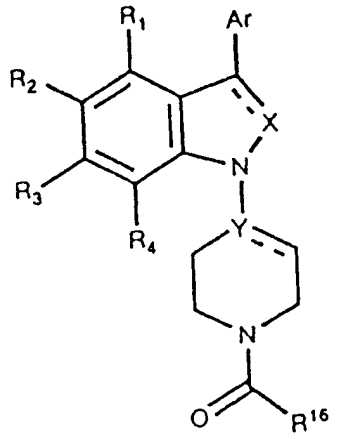


VIII

dans laquelle R^1 à R^5, X, Ar et le pointillé sont tels que définis ci-dessus, si ce n'est que R^5 ne peut pas être un hydrogène, et hal est un halogène, en cycle tétrahydropyridine ;

f) la réduction du cycle pyridinium d'un composé de formule VIII ci-dessus ou du cycle pyridyle d'un composé de formule XIV en un cycle pipéridine ;

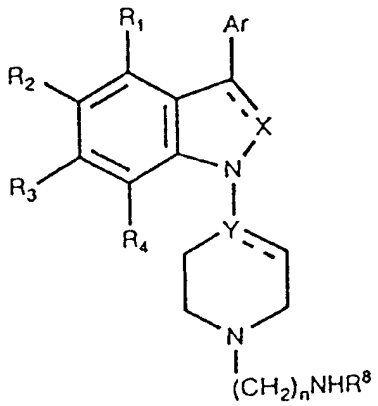
g) la réduction du groupe carbonyle d'un composé de formule suivante :



IX

dans laquelle R^1 à R^4, X, Y, Ar et les pointillés sont tels que précédemment définis et R^{15} est un hydrogène, un alkyle en C_1-C_4 ou un alcoxy en C_1-C_4 ;

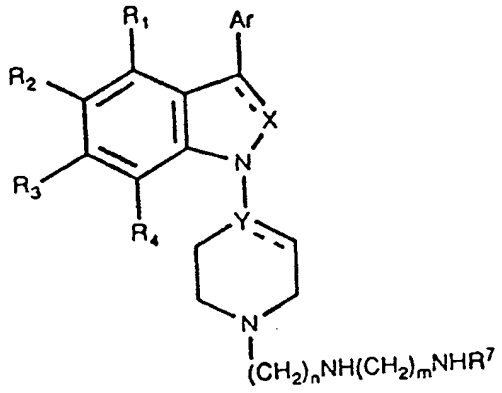
h) l'acylation d'un dérivé d'aminoalkyle de formule suivante :



X

dans laquelle R^1 à R^4, X, Y, Ar, R^8, n et les pointillés sont tels que définis ci-dessus, avec un agent d'acylation tel qu'un halogénure, un anhydride ou un anhydride mixte d'acide carboxylique, ou un chlorure de carbamyle ou de thiocarbamyle, un isocyanate, un isothiocyanate ou un chloroformiate substitué ;

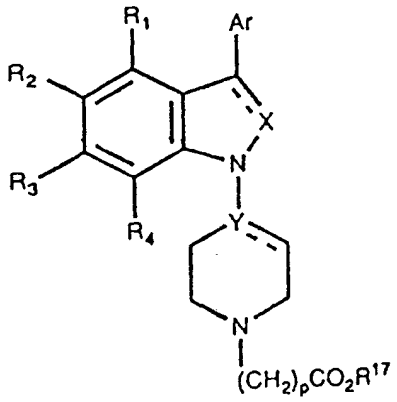
i) la réaction de cyclisation d'un dérivé intermédiaire d'éthylène-ou de propylène-diamine de formule suivante :



XI

dans laquelle R^1 à R^4, R^8, n, X, Y, Ar et les pointillés sont tels que définis ci-dessus et m est 2 ou 3, avec le phosgène, le thiophosgène ou le disulfure de carbone, pour former un substituant de structure 1a ; ou

j) la réduction d'un acide carboxylique ou d'un dérivé d'acide carboxylique de formule suivante :



XII

dans laquelle R^1 à R^4, X, Y, Ar et les pointillés sont tels que précédemment définis, R^{17} est un hydrogène ou un alkyle en C_1-C_4 et p est 1, 2 ou 3 ;

puis, si on le désire :

l'acylation d'un compose préparé dans l'un des procédés (a) à (j) répondant à la formule I dans laquelle R^5 est une structure 1a ou 1b lorsque V est NH, ou V^1 est NHR^{10}, ou U^1 est NH, avec un agent d'acylation, ou l'estérification d'un groupe hydroxy disponible dans un composé de formule I pour obtenir un précurseur de médicament ; la conversion d'un composé prépare selon l'un des procédés (a) à (j) en un sel d'addition d'acide pharmaceutiquement acceptable correspondant ; ou

le dédoublement d'un composé optiquement actif de formule I, préparé selon l'un des procédés (a) à (j), en ses isomères optiquement actifs.